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FILE COVERS 1907 - 12 Apr 2005 VOL 142 ISS 16

FILE LAST UPDATED: 11 Apr 2005 (20050411/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d stat que

L7	8401	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	TYROSINASE/BI
L9	28355	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	?MELANOMA?
L10	1728	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L9 (L) L7
L11	2088	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	XENOGEN?
L12	10	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L11 AND L10

=> d ibib abs hitrn l12 tot

L12 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:285012 HCAPLUS

DOCUMENT NUMBER: 141:138762

TITLE: CTLA-4 blockade in combination with **xenogeneic** DNA vaccines enhances T-cell responses, tumor immunity and autoimmunity to self antigens in animal and cellular model systems

AUTHOR(S): Gregor, Polly D.; Wolchok, Jedd D.; Ferrone, Cristina R.; Buchinshky, Heidi; Guevara-Patino, Jose A.; Perales, Miguel-Angel; Mortazavi, Fariborz; Bacich, Dean; Heston, Warren; Latouche, Jean-Baptiste; Sadelain, Michel; Allison, James P.; Scher, Howard I.; Houghton, Alan N.

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Vaccine (2004), 22(13-14), 1700-1708

CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Xenogeneic** DNA vaccination can elicit tumor immunity through T cell and antibody-dependent effector mechanisms. Blockade of CTLA-4 engagement with B7 expressed on APCs has been shown to enhance T cell-dependent immunity. We investigated whether CTLA-4 blockade could increase T-cell responses and tumor immunity elicited by DNA vaccines.

CTLA-4 blockade enhanced B16 tumor rejection in mice immunized against the **melanoma** differentiation antigens **tyrosinase**-related protein 2 and gp100, and this effect was stronger when anti-CTLA-4 was administered with booster vaccinations. CTLA-4 blockade also increased the T-cell responses to prostate-specific membrane antigen (PSMA) when given with the second or third vaccination. Based on these pre-clin. studies, we suggest that anti-CTLA-4 should be tested with **xenogeneic** DNA vaccines against cancer and that special attention should be given to sequence and schedule of administration.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:39019 HCAPLUS

DOCUMENT NUMBER: 140:180075

TITLE: Partial tyrosinase-specific self tolerance by HLA-A\*0201-restricted cytotoxic T lymphocytes in mice and man

AUTHOR(S): Lotz, Carina; Ferreira, Edite Antunes; Drexler, Ingo; Abdel Mutallib, Sarah; Huber, Christoph; Sutter, Gerd; Theobald, Matthias

CORPORATE SOURCE: Department of Hematology and Oncology, Johannes Gutenberg-University, Mainz, Germany

SOURCE: International Journal of Cancer (2003), Volume Date 2004, 108(4), 571-579

CODEN: IJCNAW; ISSN: 0020-7136

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The human **tyrosinase** (hTyr) (369-377) cytotoxic T lymphocyte (CTL) epitope is presented by malignant **melanoma** and various nontransformed cells in association with human leukocyte antigen (HLA)-A\*0201 (A2.1) and used for vaccination-based immunotherapy of **melanoma** patients. Its mouse homolog, mTyr (369-377), is naturally processed and bound by A2.1 with equivalent efficacy and thus enabled the authors to explore the effect of self tolerance on Tyr-specific T cells in different lines of A2.1 transgenic (Tg) mice and man. The authors found that self Tyr-reactive CTL in Tg mice and, importantly, in man were affected by partial tolerance resulting in only residual T lymphocytes of higher avidity for self Tyr along with low-avidity T cells to be present in the periphery. Immunizing mice with the **xenogeneic** nonself Tyr peptide facilitated the generation of self Tyr-reactive CTL. As compared to Tyr-reactive CTL induced by high amts. of the self Tyr epitope, however, the nonself antigen (Ag) had no effect on improving the avidity of self Tyr-specific mouse and human T cells. Depleting mice of CD25+ T cells with and without CTL-associated Ag 4 (CTLA-4) blockade demonstrated that tolerance of Tyr-specific CTL was not regulated by CD4+CD25+ T regulatory cells (Treg) or CTLA-4. The authors' studies have important implications for the design of anti-Tyr-based immunotherapeutics.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:273846 HCAPLUS

DOCUMENT NUMBER: 139:358123

TITLE: Long-Term Survival of Dogs with Advanced Malignant **Melanoma** after DNA Vaccination with **Xenogeneic** Human **Tyrosinase**: A Phase I Trial

AUTHOR(S): Bergman, Philip J.; McKnight, Joanne; Novosad, Andrew; Charney, Sarah; Farrelly, John; Craft, Diane; Wulderk, Michelle; Jeffers, Yusuf; Sadelain, Michel; Hohenhaus, Ann E.; Segal, Neil; Gregor, Polly; Engelhorn, Manuel; Riviere, Isabelle; Houghton, Alan N.; Wolchok, Jedd D.

CORPORATE SOURCE: Donaldson-Atwood Cancer Clinic and Flaherty Comparative Oncology Laboratory, The E&M Bobst Hospital of the Animal Medical Center, New York, NY, 10021, USA

SOURCE: Clinical Cancer Research (2003), 9(4), 1284-1290  
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Canine malignant **melanoma** (CMM) is a spontaneous, aggressive, and metastatic neoplasm. Preclin. mouse studies have shown that **xenogeneic** DNA vaccination with genes encoding **tyrosinase** family members can induce antibody and cytotoxic T-cell responses, resulting in tumor rejection. These studies provided the rationale for a trial of **xenogeneic** DNA vaccination in CMM using the human **tyrosinase** gene. Three cohorts of three dogs each with advanced (WHO stage II, III, or IV) CMM received four biweekly i.m. injections (dose levels 100, 500, or 1500 µg, resp./vaccination) of human **tyrosinase** plasmid DNA i.m. via the Biojector2000 delivery device. Mild local reactions at injection sites were the only toxicities observed, with no signs of autoimmunity. One dog with stage IV disease had a complete clin. response in multiple lung metastases for 329 days. Two dogs with stage IV disease had long-term survivals (421 and 588+ days) in the face of significant bulky metastatic disease, and two other dogs with locally controlled stage II/III disease had long-term survivals (501 and 496 days) with no evidence of **melanoma** on necropsy. Four other dogs were euthanized because of progression of the primary tumor. The Kaplan-Meier median survival time for all nine dogs was 389 days. The results of this trial demonstrate that **xenogeneic** DNA vaccination of dogs with advanced malignant **melanoma** is a safe and potentially therapeutic modality. On the basis of these results, addnl. evaluation of this novel therapeutic is warranted in locally controlled CMM and advanced human **melanoma**.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:794136 HCAPLUS

DOCUMENT NUMBER: 137:309482

TITLE: Compositions for treatment of melanoma and method of using same

INVENTOR(S): Houghton, Alan N.; Bergman, Philip J.; Wolchok, Jedd D.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U. S. Ser. No. 627,694.  
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 2002150589	A1	20021017	US 2001-996128	20011127
WO 9825574	A2	19980618	WO 1997-US22669	19971210
WO 9825574	A3	19980903		

W: CA, JP, US

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 6328969	B1	20011211	US 1999-308697	19990521
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PRIORITY APPLN. INFO.:

US 1996-32535P	P	19961210
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US 1997-36419P	P	19970217
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WO 1997-US22669	W	19971210
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US 1999-308697	A2	19990521
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US 2000-180651P	P	20000126
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US 2000-627694	A2	20000728
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AB Melanoma can be treated in a mammalian subject by administering to the subject an immunol.-effective amount of a **xenogeneic** melanoma-associated differentiation antigen. For example, genetic immunization with a plasmid containing a sequence encoding human gp75 has been shown to be effective in treatment of dogs with melanoma.

L12 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:43903 HCAPLUS

DOCUMENT NUMBER: 137:92289

TITLE: **Xenogeneic** DNA Immunization in Melanoma Models for Minimal Residual Disease

AUTHOR(S): Hawkins, William G.; Gold, Jason S.; Blachere, Nathalie E.; Bowne, Wilbur B.; Hoos, Axel; Lewis, Jonathan J.; Houghton, Alan N.

CORPORATE SOURCE: Swim Across America Laboratory, Departments of Surgery &amp; Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Journal of Surgical Research (2002), 102(2), 137-143  
CODEN: JSGRA2; ISSN: 0022-4804

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Introduction. DNA immunization with **xenogeneic** genes encoding homologous antigens protects mice against tumor challenge with syngeneic melanoma in a lung metastasis model. The effect of **xenogeneic** human TRP-2 (hTRP2) DNA immunization on disease confined to an orthotopic site, the skin, and in a model of minimal residual disease that is relevant to a setting of adjuvant therapy for micrometastatic cancer is reported. Methods. Immunization and tumor challenge with B16F10LM3 melanoma were performed in C57BL/6 mice and in mice genetically deficient in MHC class I or II mols. A melanoma variant of B16 with a predilection for lung metastasis was selected and used to challenge C57BL/6 mice. Tumor challenge in the footpad with the B16 variant was followed by local tumor growth and lung metastasis. The tumor-bearing distal extremities were surgically resected and mice were randomized to receive hTRP2 DNA immunization or no treatment. Approx. 3-5 wk after surgical resection, lungs were harvested and metastases counted. Results. **Xenogeneic** DNA immunization with hTRP2 prevented tumor growth in the skin by a mechanism requiring CD4+ and CD8+ T cells but did not inhibit the growth of established tumors. Adjuvant immunization with hTRP2 DNA after resection significantly reduced lung metastases and decreased local recurrence rates after surgical resection. Conclusions. **Xenogeneic** DNA immunization with hTRP2 was effective in protecting mice from intradermal tumor challenge. Immunization prevented local recurrence and the development of metastases in a mouse model of minimal residual disease, supporting a role for DNA immunization against melanosomal antigens as an adjuvant to surgery in high-risk primary

melanomas. (c) 2002 Academic Press.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:34713 HCAPLUS

DOCUMENT NUMBER: 134:206312

TITLE: Dendritic cells break tolerance and induce protective immunity against a melanocyte differentiation antigen in an autologous melanoma model

AUTHOR(S): Schreurs, Marco W. J.; Eggert, Andreas A. O.; De Boer, Annemiek J.; Vissers, Joost L. M.; Van Hall, Thorbald; Offringa, Rienk; Figdor, Carl G.; Adema, Gosse J.

CORPORATE SOURCE: Department of Immunology, The Netherlands Cancer Institute, Amsterdam, 1066 CX, Neth.

SOURCE: Cancer Research (2000), 60(24), 6995-7001

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Tyrosinase**-related protein (TRP) 2 belongs to the melanocyte differentiation antigens and has been implicated as a target for immunotherapy of human as well as murine **melanoma**. In the current report, the authors explored the efficacy of non-mutated epitopes with differential binding affinity for MHC class I, derived from mouse TRP2 to induce CTL-mediated, tumor-reactive immunity in vivo within the established B16 **melanoma** model of C57BL/6 mice. The use of non-mutated TRP2-derived epitopes for vaccination provides a mouse model that closely mimics human **melanoma** without introduction of **xenogeneic** or otherwise foreign antigen. The results demonstrate that vaccination with TRP2 peptide-loaded bone marrow-derived dendritic cells (DCs) results in activation of high avidity TRP2-specific CTLs, displaying lytic activity against both B16 **melanoma** cells and normal melanocytes in vitro. In vivo, protective antitumor immunity against a lethal s.c. B16 challenge was observed upon DC-based vaccination in this fully autologous tumor model. The level of protective immunity pos. correlated with the MHC class I binding capacity of the peptides used for vaccination. In contrast, within this autologous model, vaccination with TRP2 peptide in Freund's adjuvant or TRP2-encoding plasmid DNA did not result in protective immunity against B16. Strikingly, despite the observed CTL-mediated melanocyte destruction in vitro, melanocyte destruction in vivo was sporadic and primarily restricted to minor depigmentation of the vaccination site. These results emphasize the potency of DC-based vaccines to induce immunity against autologous tumor-associated antigen and indicate that CTL-mediated antitumor immunity can proceed without development of adverse autoimmunity against normal tissue.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:617875 HCAPLUS

DOCUMENT NUMBER: 133:295014

TITLE: Relevance of the tumor antigen in the validation of three vaccination strategies for melanoma

AUTHOR(S): Bellone, Matteo; Cantarella, Daniela; Castiglioni, Paola; Crosti, Maria Cristina; Ronchetti, Anna; Moro, Monica; Garancini, Maria Paola; Casorati, Giulia; Dellabona, Paolo

CORPORATE SOURCE: Laboratory of Tumor Immunology, Cancer Immunotherapy

and Gene Therapy Program, H. San Raffaele Scientific  
Institute, Milan, 20132, Italy  
SOURCE: Journal of Immunology (2000), 165(5), 2651-2656  
CODEN: JOIMA3; ISSN: 0022-1767  
PUBLISHER: American Association of Immunologists  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Many preclin. studies of cancer immunotherapy are based on the testing of a single vaccination strategy in several tumor models. Moreover, most of those studies used **xenogeneic** Ags, which, owing to their high immunogenicity, may not represent realistic models for the validation of cancer immunotherapies. To address these issues, the authors compared the vaccination efficacy of three well established strategies (i.e., naked DNA; peptide-pulsed dendritic cells (DC), or a mixture of peptide and the Escherichia coli toxin LTR72) using the **xenogeneic** OVA or the naturally expressed **tyrosinase**-related protein 2 (TRP-2) tumor Ag in the B16 **melanoma** model. C57BL/6 mice received one to three s.c. injections of peptide-pulsed DC or DNA, or one to four mucosal administrations of peptide-toxin mixture. One to 2 wk later, the animals were challenged s.c. with B16 or B16 cells expressing OVA (B16-OVA). Vaccination of mice with OVA induced in all cases **melanoma**-specific CTL and protection against B16-OVA. When TRP-2 was used, all three vaccines elicited B16-specific CTL, but only DC pulsed with the immunodominant T cell epitope TRP-2181-188 allowed protection against B16. Even more importantly, a vaccination regimen with TRP-2-pulsed DC, started 24 h after the injection of a lethal number of B16 cells, caused a therapeutic effect in 60% of the challenged animals. Our results strongly emphasize the relevance of the tumor Ag in the definition of immunotherapeutic strategies for cancer, and support the use of peptide-pulsed DC as cancer vaccine in humans.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:203364 HCAPLUS

DOCUMENT NUMBER: 133:206512

TITLE: Genetic immunization of mice with human **tyrosinase**-related protein 2: implications for the immunotherapy of **melanoma**

AUTHOR(S): Steitz, Julia; Bruck, Jurgen; Steinbrink, Kerstin; Enk, Alexander; Knop, Jurgen; Tuting, Thomas

CORPORATE SOURCE: Department of Dermatology, J. Gutenberg-University, Mainz, D-55101, Germany

SOURCE: International Journal of Cancer (2000), 86(1), 89-94  
CODEN: IJCNAA; ISSN: 0020-7136

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The melanosomal protein TRP2 expressed by melanocytes and most melanoma cells is an attractive, clin. relevant model antigen for the exptl. development of melanoma immunotherapy in mice. A peptide shared by murine and human TRP2 can be recognized by melanoma-reactive CTL in C57BL/6 mice, as well as in human melanoma patients. Previous expts. demonstrated that gene gun immunization of mice with plasmid DNA encoding autologous murine TRP2 was unable to induce protective immunity against B16 melanoma cells naturally expressing TRP2. In the present study, we investigated whether the use of cDNA encoding **xenogeneic** human TRP2, which is highly homologous to murine TRP2, would be more effective. Genetic immunization of mice with human TRP2 resulted in coat depigmentation as a sign of

autoimmune-mediated destruction of melanocytes and provided significant protection against metastatic growth of B16 melanoma. Induction of protective immunity was associated with TRP2-reactive antibodies and CD8+ T cells. Furthermore, immunization with recombinant adenovirus was more effective than immunization with plasmid DNA using the gene gun. Our results provide new insights for the development of antigen-specific immunotherapy of melanoma.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:799448 HCAPLUS

DOCUMENT NUMBER: 132:92212

TITLE: Coupling and uncoupling of tumor immunity and autoimmunity

AUTHOR(S): Bowne, Wilbur B.; Srinivasan, Roopa; Wolchok, Jedd D.; Hawkins, William G.; Blachere, Nathalie E.; Dyall, Ruben; Lewis, Jonathan J.; Houghton, Alan N.

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Journal of Experimental Medicine (1999), 190(11), 1717-1722

CODEN: JEMEAV; ISSN: 0022-1007

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Self-antigens, in the form of differentiation antigens, are commonly recognized by the immune system on **melanoma** and other cancers. We have shown previously that active immunization of mice against the melanocyte differentiation antigen, a **tyrosinase**-related protein (TRP) gp75TRP-1 (the brown locus protein) expressed by **melanomas**, could induce tumor immunity and autoimmunity manifested as depigmentation. In this system, tumor immunity and autoimmunity were mediated by autoantibodies. Here, we characterize immunity against another **tyrosinase** family glycoprotein TRP-2 (the slaty locus protein), using the same mouse model and method of immunization. As observed previously for gp75TRP-1, immunity was induced by DNA immunization against a **xenogeneic** form of TRP-2, but not against the syngeneic gene, and depended on CD4+ cells. Immunization against TRP-2 induced autoantibodies and autoreactive cytotoxic T cells. In contrast to immunization against gp75TRP-1, both tumor immunity and autoimmunity required CD8+ T cells, but not antibodies. Only autoimmunity required perforin, whereas tumor immunity proceeded in the absence of perforin. Thus, immunity induced against two closely related autoantigens that are highly conserved throughout vertebrate evolution involved qual. different mechanisms, i.e., antibody vs. CD8+ T cell. However, both pathways led to tumor immunity and identical phenotypic manifestations of autoimmunity.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:747477 HCAPLUS

DOCUMENT NUMBER: 126:30063

TITLE: Immune response to a differentiation antigen induced by altered antigen: a study of tumor rejection and autoimmunity

AUTHOR(S): Naftzger, Clarissa; Takechi, Yoshizumi; Kohda, Hironobu; Hara, Isao; Vijayasaradhi, Setaluri; Houghton, Alan N.

CORPORATE SOURCE: Swim Across America Lab., Memorial Sloan-Kettering  
Cancer Cent., New York, NY, 10021, USA  
SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America (1996), 93(25), 14809-14814  
CODEN: PNASA6; ISSN: 0027-8424  
PUBLISHER: National Academy of Sciences  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Recognition of self is emerging as a theme for the immune recognition of human cancer. One question is whether the immune system can actively respond to normal tissue autoantigens expressed by cancer cells. A second but related question is whether immune recognition of tissue autoantigens can actually induce tumor rejection. To address these issues, a mouse model was developed to investigate immune responses to a melanocyte differentiation antigen, **tyrosinase**-related protein 1 (or gp75), which is the product of the brown locus. In mice, immunization with purified syngeneic gp75 or syngeneic cells expressing gp75 failed to elicit antibody or cytotoxic T-cell responses to gp75, even when different immune adjuvants and cytokines were included. However, immunization with altered sources of gp75 antigen, in the form of either syngeneic gp75 expressed in insect cells or human gp75, elicited autoantibodies to gp75. Immunized mice rejected metastatic **melanomas** and developed patchy depigmentation in their coats. These studies support a model of tolerance maintained to a melanocyte differentiation antigen where tolerance can be broken by presenting sources of altered antigen (e.g., homologous **xenogeneic** protein or protein expressed in insect cells). Immune responses induced with these sources of altered antigen reacted with various processed forms of native, syngeneic protein and could induce both tumor rejection and autoimmunity.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2 134 SEA FILE=HCAPLUS ABB=ON PLU=ON ("HOUGHTON ALAN"/AU OR  
"HOUGHTON ALAN N"/AU)  
L3 71 SEA FILE=HCAPLUS ABB=ON PLU=ON ("BERGMAN P"/AU OR "BERGMAN P  
J"/AU)  
L4 8 SEA FILE=HCAPLUS ABB=ON PLU=ON ("BERGMAN PHILIP J"/AU OR  
"BERGMAN PHILIP JOHN"/AU)  
L5 33 SEA FILE=HCAPLUS ABB=ON PLU=ON ("WOLCHOK J D"/AU OR "WOLCHOK  
JEDD"/AU OR "WOLCHOK JEDD D"/AU OR "WOLCHOK JEDD DAVID"/AU)  
L15 21 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (L3 OR L4 OR L5)

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L15 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2005:103365 HCAPLUS  
DOCUMENT NUMBER: 142:296365  
TITLE: CD8+ T-cell-dependent immunity following xenogeneic  
DNA immunization against CD20 in a tumor challenge  
model of B-cell lymphoma  
AUTHOR(S): Palomba, Maria Lia; Roberts, Wendy K.; Dao, Tao;  
Manukian, Gregory; Guevara-Patino, Jose A.;  
**Wolchok, Jedd D.**; Scheinberg, David A.;  
**Houghton, Alan N.**

CORPORATE SOURCE: Department of Medicine and Immunology Program,  
Memorial Sloan-Kettering Cancer Center, New York, NY,  
USA

SOURCE: Clinical Cancer Research (2005), 11(1), 370-379  
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The CD20 B-cell differentiation antigen is an attractive target for immunotherapy of B-cell lymphomas. In an exptl. lymphoma model, BALB/c mice were immunized with mouse or human CD20 cDNA (mCD20 and hCD20, resp.) or their extracellular domains (minigenes). IFN $\gamma$  secretion by CD8+ T cells against CD20 was detected in mice vaccinated with hCD20 or human minigene, indicating that hCD20-primed CD8+ T cells recognize syngeneic CD20. Systemic challenge with syngeneic A20 cells, an aggressive lymphoma, resulted in long-term survival in a subset of immunized mice. Overall long-term survival was 14% in groups vaccinated with the human minigene vs. 4% in control groups. CD8+ T-cell depletion during the effector phase completely abrogated this effect. Antibodies against a recombinant mouse CD20 protein produced in insect cells were detected in mice immunized with hCD20 DNA and human and mouse minigene, but not in mice receiving mCD20 DNA. These results show that active immunization with xenogeneic DNA vaccines can induce CD8+ T cell-dependent immunity against CD20.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:962789 HCAPLUS

DOCUMENT NUMBER: 142:211646

TITLE: Phase II study of temozolomide plus thalidomide for the treatment of metastatic melanoma

AUTHOR(S): Hwu, Wen-Jen; Krown, Susan E.; Menell, Jennifer H.; Panageas, Katherine S.; Merrell, Janene; Lamb, Lynne A.; Williams, Linda J.; Quinn, Carolyn J.; Foster, Theresa; Chapman, Paul B.; Livingston, Philip O.; **Wolchok, Jedd D.; Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, USA

SOURCE: Journal of Clinical Oncology (2003), 21(17), 3351-3356  
CODEN: JCONDN; ISSN: 0732-183X

PUBLISHER: American Society of Clinical Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim was to further investigate the efficacy and safety of temozolomide plus thalidomide in patients with metastatic melanoma without brain metastases. Patients with histol. confirmed advanced-stage metastatic melanoma were enrolled in an open-label, phase II study. The primary end point was response rate. Patients received temozolomide (75 mg/m<sup>2</sup>/d + 6 wk with a 2-wk rest between cycles) plus concomitant thalidomide (200 mg/d with dose escalation to 400 mg/d for patients < 70 years old, or 100 mg/d with dose escalation to 250 mg/d for patients  $\geq$  70 years old). Treatment was continued until unacceptable toxicity or disease progression occurred. Thirty-eight patients (median age, 62 years) with stage IV (three patients with M1a, eight with M1b, and 26 with M1c) or stage IIIC (one patient) melanoma and a median of four metastatic sites were enrolled, and received a median of two cycles of therapy. Twelve patients (32%) had an objective tumor response, including one with an ongoing complete response of 25+ months' duration and 11 with partial

responses. Five patients achieving partial response with a more than 90% reduction of disease were converted to a complete response with surgery. Treatment was generally well tolerated. Median survival was 9.5 mo (95% confidence interval, 6.05 to 19.38 mo), with a median follow-up among survivors of 24.3 mo. The combination of temozolomide plus thalidomide seems to be a promising and well-tolerated oral regimen for metastatic melanoma that merits further study.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:941945 HCAPLUS

DOCUMENT NUMBER: 142:4421

TITLE: Classification of clear-cell sarcoma as a subtype of melanoma by genomic profiling

AUTHOR(S): Segal, Neil H.; Pavlidis, Paul; Noble, William S.; Antonescu, Cristina R.; Viale, Agnes; Wesley, Umadevi V.; Busam, Klaus; Gallardo, Humilidad; DeSantis, Dianne; Brennan, Murray F.; Cordon-Cardo, Carlos; **Wolchok, Jedd D.; Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and Columbia Genome Center, Columbia University, New York, NY, USA

SOURCE: Journal of Clinical Oncology (2003), 21(9), 1775-1781  
CODEN: JCONDN; ISSN: 0732-183X

PUBLISHER: American Society of Clinical Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: To develop a genome-based classification scheme for clear-cell sarcoma (CCS), also known as melanoma of soft parts (MSP), which would have implications for diagnosis and treatment. This tumor displays characteristic features of soft tissue sarcoma (STS), including deep soft tissue primary location and a characteristic translocation, t(12;22)(q13;q12), involving EWS and ATF1 genes. CCS/MSP also has typical melanoma features, including immunoreactivity for S100 and HMB45, pigmentation, MITF-M expression, and a propensity for regional lymph node metastases. Materials and Methods: RNA samples from 21 cell lines and 60 pathol. confirmed cases of STS, melanoma, and CCS/MSP were examined using the U95A GeneChip (Affymetrix, Santa Clara, CA). Hierarchical cluster anal., principal component anal., and support vector machine (SVM) anal. exploited genomic correlations within the data to classify CCS/MSP. Results: Unsupervised analyses demonstrated a clear distinction between STS and melanoma and, furthermore, showed that CCS/MSP cluster with the melanomas as a distinct group. A supervised SVM learning approach further validated this finding and provided a user-independent approach to diagnosis. Genes of interest that discriminate CCS/MSP included those encoding melanocyte differentiation antigens, MITF, SOX10, ERBB3, and FGFR1. Conclusion: Gene expression profiles support the classification of CCS/MSP as a distinct genomic subtype of melanoma. Anal. of these gene profiles using the SVM may be an important diagnostic tool. Genomic anal. identified potential targets for the development of therapeutic strategies in the treatment of this disease.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:285012 HCAPLUS

DOCUMENT NUMBER: 141:138762

TITLE: CTLA-4 blockade in combination with xenogeneic DNA vaccines enhances T-cell responses, tumor immunity and

autoimmunity to self antigens in animal and cellular model systems

AUTHOR(S): Gregor, Polly D.; **Wolchok, Jedd D.**; Ferrone, Cristina R.; Buchinshky, Heidi; Guevara-Patino, Jose A.; Perales, Miguel-Angel; Mortazavi, Fariborz; Bacich, Dean; Heston, Warren; Latouche, Jean-Baptiste; Sadelain, Michel; Allison, James P.; Scher, Howard I.; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Vaccine (2004), 22(13-14), 1700-1708  
CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Xenogeneic DNA vaccination can elicit tumor immunity through T cell and antibody-dependent effector mechanisms. Blockade of CTLA-4 engagement with B7 expressed on APCs has been shown to enhance T cell-dependent immunity. We investigated whether CTLA-4 blockade could increase T-cell responses and tumor immunity elicited by DNA vaccines. CTLA-4 blockade enhanced B16 tumor rejection in mice immunized against the melanoma differentiation antigens tyrosinase-related protein 2 and gp100, and this effect was stronger when anti-CTLA-4 was administered with booster vaccinations. CTLA-4 blockade also increased the T-cell responses to prostate-specific membrane antigen (PSMA) when given with the second or third vaccination. Based on these pre-clin. studies, we suggest that anti-CTLA-4 should be tested with xenogeneic DNA vaccines against cancer and that special attention should be given to sequence and schedule of administration.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:192946 HCAPLUS

DOCUMENT NUMBER: 140:355335

TITLE: Immunity to cancer through immune recognition of altered self: studies with melanoma

AUTHOR(S): Guevara-Patino, Jose A.; Turk, Mary Jo; **Wolchok, Jedd D.**; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and the Weill Graduate School of Medical Sciences, Medical School of Cornell University, New York, NY, 10021, USA

SOURCE: Advances in Cancer Research (2003), 90, 157-177, 1 plate  
CODEN: ACRSAJ; ISSN: 0065-230X

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The adaptive immune system is capable of recognizing cancer through T and B-cell receptors. However, priming adaptive immunity against self antigens is potentially a difficult task. Presentation of altered self to the immune system is a strategy to elicit immunity against poorly immunogenic antigens. We have shown that immunization with conserved paralogues of tumor antigens can induce adaptive immunity against self antigens expressed by cancer. Remarkably, cancer immunity elicited by closely related paralogues can generate distinct adaptive immune responses, either antibody or T-cell dependent. Cancer immunity induced by xenogeneic immunization follows multiple and alternative pathways. The effector phase of tumor immunity can be mediated by

cytotoxic T cells or macrophages and perhaps natural killer cells for antibody-dependent immunity. Helper CD4+ T cells are typically, but not always, required to generate immunity. Autoimmunity is frequently observed following immunization. Cancer immunity and autoimmunity use overlapping mechanisms, and therefore they are difficult to uncouple, but distinct pathways can be discerned that open the eventual possibility of uncoupling tumor immunity from autoimmunity. Studies examining the mol. basis for immunogenicity of conserved paralogues are facilitating the development of new strategies to rationally design vaccines that trigger adaptive immune responses to cancer.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:971282 HCAPLUS

DOCUMENT NUMBER: 140:26899

TITLE: Method and compositions for stimulation of an immune response to CD20 using a xenogeneic CD20 antigen

INVENTOR(S): Palomba, Maria Lia; **Houghton, Alan;**  
**Wolchok, Jedd;** Scheinberg, David A.; Roberts, Wendy K.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S. Ser. No. 627,694.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003228326	A1	20031211	US 2002-285874	20021031
WO 9825574	A2	19980618	WO 1997-US22669	19971210
WO 9825574	A3	19980903		

W: CA, JP, US

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 6328969	B1	20011211	US 1999-308697	19990521
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PRIORITY APPLN. INFO.:

US 1997-36419P	P	19970217
US 1999-308697	A2	19970217
WO 1997-US22669	W	19971210
US 2000-627694	A2	20000728
US 1996-32535P	P	19961210

AB Tolerance of the immune system for endogenous CD20 can be overcome and an immune response stimulated by administration of xenogeneic or xenoexpressed CD20 antigen. For example, mouse CD20, or antigenically-effective portions thereof, can be used to stimulate an immune response to the corresponding differentiation antigen in a human subject. Administration of xenogeneic antigens in accordance with the invention results in an effective immunity against CD20 expressed by the cancer in the treated individual, thus providing a therapeutic approach to the treatment of lymphomas and leukemia expressing CD20. For production of a recombinant mouse CD20 fusion protein (recCD20) the inventors used the baculovirus expression system to obtain a partially purified recCD20 for the use as xenoexpressed CD20.

L15 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:690210 HCAPLUS

DOCUMENT NUMBER: 139:306210

TITLE: GM-CSF DNA induces specific patterns of cytokines and chemokines in the skin: implications for DNA vaccines

AUTHOR(S): Perales, Miguel-Angel; Fantuzzi, Giamila; Goldberg, Stacie M.; Turk, Mary Jo; Mortazavi, Fariborz; Busam, Klaus; **Houghton, Alan N.**; Dinarello, Charles A.; **Wolchok, Jedd D.**

CORPORATE SOURCE: The Swim Across America Laboratory, Memorial Sloan-Kettering Cancer Center and Weill Graduate School of Medical Sciences of Cornell University, New York, USA

SOURCE: Cytokines, Cellular & Molecular Therapy (2002), 7(3), 125-133  
CODEN: CCMTFO; ISSN: 1368-4736

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances immune responses by inducing the proliferation, maturation, and migration of dendritic cells, and the expansion and differentiation of B and T lymphocytes. Similar biol. effects have been observed with the use of GM-CSF DNA in mouse models for therapy of cancer and infectious diseases, and its use is currently being investigated in clin. trials in combination with DNA vaccines. To further understand the adjuvant mechanisms of GM-CSF DNA, we examined early events following its administration. We found measurable levels of GM-CSF protein in the skin and muscle, as well as in serum. Measurements of other cytokine and chemokine levels revealed differential expression patterns over time. The early response was characterized by high levels of inflammatory mol.s., including IL-1 $\beta$ , IL-6, TNF $\alpha$ , RANTES, MIP-1 $\alpha$  and MCP-1, later followed by expression of precursor Th1 cytokines, IL-12 and IL-18, concomitant with IFN $\gamma$  production. Local production of GM-CSF protein also resulted in the early recruitment of polymorphonuclear cells and later recruitment of mononuclear cells, including dendritic cells. These results have implications for understanding early events in the immune response to DNA vaccines, and provide a basis for development of new approaches to cancer vaccines, including the use of cytokine genes as adjuvants.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:429991 HCAPLUS

DOCUMENT NUMBER: 139:163255

TITLE: Immunity to melanoma: unraveling the relation of tumor immunity and autoimmunity

AUTHOR(S): Ramirez-Montagut, Teresa; Turk, Mary Jo; **Wolchok, Jedd D.**; Guevara-Patino, Jose A.; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, Weill Graduate School of Medical Sciences of Cornell University, New York, NY, 10021, USA

SOURCE: Oncogene (2003), 22(20), 3180-3187  
CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Cancer cells express self-antigens that are weakly recognized by the immune system. Even though responses against autologous cells are difficult to induce, the immune system is still able to mount a response against cancer. The discovery of the mol. identity of antigens that are

recognized by the immune system of melanoma patients has led to the elucidation of tumor immunity at a cellular and mol. level. Multiple pathways in both the priming and effector phases of melanoma rejection have been described. Animal models' active immunotherapies for melanoma show a requirement for the cellular compartment of the immune system in the priming phase, primarily CD4+T cells. More diverse elements are required for the effector phase, including components from the innate immune system (macrophages, complement and/or natural killer cells) and from the adaptive immune system (CD8+ T cells and B cells). Minor differences in amino-acid sequences of antigens must determine the particular mechanisms involved in tumor rejection. Since the immune system contains T and B cells that recognize and reject autologous cells, a consequence of tumor immunity is potential autoimmunity. There are distinct pathways for tumor immunity and autoimmunity. The requirements for autoimmunity at the priming phase seem to be CD4+/IFN- $\gamma$  dependent while the effector mechanisms are alternative and redundant. Vitiligo (autoimmune hypopigmentation) can be mediated by T cells, Fc $\gamma$ R+ macrophages and/or complement.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:345937 HCAPLUS

DOCUMENT NUMBER: 139:34865

TITLE: A Single Heteroclitic Epitope Determines Cancer Immunity After Xenogeneic DNA Immunization Against a Tumor Differentiation Antigen

AUTHOR(S): Gold, Jason S.; Ferrone, Cristina R.; Guevara-Patino, Jose A.; Hawkins, William G.; Dyall, Ruben; Engelhorn, Manuel E.; Wolchok, Jedd D.; Lewis, Jonathan J.; Houghton, Alan N.

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, Cornell University, New York, NY, 10021, USA

SOURCE: Journal of Immunology (2003), 170(10), 5188-5194  
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Successful active immunization against cancer requires induction of immunity against self or mutated self Ags. However, immunization against self Ags is difficult. Xenogeneic immunization with orthologous Ags induces cancer immunity. The present study evaluated the basis for immunity induced by active immunization against a melanoma differentiation Ag, gp100. Tumor rejection of melanoma was assessed after immunization with human gp100 (hgpl00) DNA compared with mouse gp100 (mgpl00). C57BL/6 mice immunized with xenogeneic full-length hgpl00 DNA were protected against syngeneic melanoma challenge. In contrast, mice immunized with hgpl00 DNA and given i.p. tolerizing doses of the hgpl00 Db-restricted peptide, hgpl0025-33, were incapable of rejecting tumors. Furthermore, mice immunized with DNA constructs of hgpl00 in which the hgpl0025-27 epitope was substituted with the weaker Db-binding epitope from mgpl00 (mgpl0025-27) or a mutated epitope unable to bind Db did not reject B16 melanoma. Mice immunized with a minigene construct of hgpl0025-33 rejected B16 melanoma, whereas mice immunized with the mgpl0025-33 minigene did not develop protective tumor immunity. In this model of xenogeneic DNA immunization, the presence of an hgpl00 heteroclitic epitope with a higher affinity for MHC created by three amino acid (25 to 27) substitutions at predicted minor anchor residues was necessary and sufficient to induce protective tumor immunity in H-2b mice with melanoma.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:273846 HCAPLUS

DOCUMENT NUMBER: 139:358123

TITLE: Long-Term Survival of Dogs with Advanced Malignant Melanoma after DNA Vaccination with Xenogeneic Human Tyrosinase: A Phase I Trial

AUTHOR(S): **Bergman, Philip J.**; McKnight, Joanne; Novosad, Andrew; Charney, Sarah; Farrelly, John; Craft, Diane; Wulderk, Michelle; Jeffers, Yusuf; Sadelain, Michel; Hohenhaus, Ann E.; Segal, Neil; Gregor, Polly; Engelhorn, Manuel; Riviere, Isabelle; **Houghton, Alan N.**; **Wolchok, Jedd D.**

CORPORATE SOURCE: Donaldson-Atwood Cancer Clinic and Flaherty Comparative Oncology Laboratory, The E&M Bobst Hospital of the Animal Medical Center, New York, NY, 10021, USA

SOURCE: Clinical Cancer Research (2003), 9(4), 1284-1290  
CODEN: CCREP4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Canine malignant melanoma (CMM) is a spontaneous, aggressive, and metastatic neoplasm. Preclin. mouse studies have shown that xenogeneic DNA vaccination with genes encoding tyrosinase family members can induce antibody and cytotoxic T-cell responses, resulting in tumor rejection. These studies provided the rationale for a trial of xenogeneic DNA vaccination in CMM using the human tyrosinase gene. Three cohorts of three dogs each with advanced (WHO stage II, III, or IV) CMM received four biweekly i.m. injections (dose levels 100, 500, or 1500 µg, resp./vaccination) of human tyrosinase plasmid DNA i.m. via the Biojector2000 delivery device. Mild local reactions at injection sites were the only toxicities observed, with no signs of autoimmunity. One dog with stage IV disease had a complete clin. response in multiple lung metastases for 329 days. Two dogs with stage IV disease had long-term survivals (421 and 588+ days) in the face of significant bulky metastatic disease, and two other dogs with locally controlled stage II/III disease had long-term survivals (501 and 496 days) with no evidence of melanoma on necropsy. Four other dogs were euthanized because of progression of the primary tumor. The Kaplan-Meier median survival time for all nine dogs was 389 days. The results of this trial demonstrate that xenogeneic DNA vaccination of dogs with advanced malignant melanoma is a safe and potentially therapeutic modality. On the basis of these results, addnl. evaluation of this novel therapeutic is warranted in locally controlled CMM and advanced human melanoma.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:166483 HCAPLUS

DOCUMENT NUMBER: 138:336082

TITLE: The role of lipopolysaccharide in T-cell responses following DNA vaccination

AUTHOR(S): Hawkins, William G.; Trcka, Jiri; Segal, Neil; Blachere, Nathalie E.; Gold, Jason S.; Moroi, Yoichi; Bowne, Wilbur B.; Lewis, Jonathan J.; **Wolchok, Jedd D.**; **Houghton, Alan N.**

CORPORATE SOURCE: Swim Across America Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Vaccine (2003), 21(13-14), 1548-1553  
CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Bacterial products, including lipopolysaccharide (LPS), are potential impurities in plasmid DNA vaccines. LPS has immunostimulatory properties even at exceedingly low concns. through activation of Toll-like receptor 4 (TLR4). The potency of T-cell responses after vaccination was tested with DNA containing high LPS or depleted of LPS in TLR4-competent and TLR4-deficient mice. CD8+ T-cell responses were readily induced in TLR4-deficient mice immunized with DNA depleted of LPS. LPS in DNA vaccines is not required for CD8+ T-cell responses.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:967908 HCAPLUS

DOCUMENT NUMBER: 138:151745

TITLE: Multiple pathways to tumor immunity and concomitant autoimmunity

AUTHOR(S): Turk, Mary Jo; **Wolchok, Jedd D.**;  
Guevara-Patino, Jose A.; Goldberg, Stacie M.;  
**Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and the Weill Graduate School of Medical Sciences of Cornell University, New York, NY, USA

SOURCE: Immunological Reviews (2002), 188, 122-135  
CODEN: IMRED2; ISSN: 0105-2896

PUBLISHER: Blackwell Munksgaard

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The immune repertoire contains T cells and B cells that can recognize autologous cancer cells. This repertoire is directed against self, and in some cases altered self (mutations). Priming immune responses against self antigens can be difficult. Strategies are presented using altered self to elicit immunity against self in poorly immunogenic tumor models. Mechanisms underlying immunity to self antigens on cancer cells show that the immune system can use diverse strategies for cancer immunity, in both the immunization and the effector phases. CD4+ T cells are typically, but not always, required for immunization. The effector phase of tumor immunity can involve cytotoxic T cells, macrophages with activating Fc receptors, and/or killer domain mols. This diversity in the effector phase is observed even when immunizing with conserved paralogs. A consequence of tumor immunity is potentially autoimmunity, which may be undesirable. Autoimmunity uses similar mechanisms as tumor immunity, but tumor immunity and autoimmunity can uncouple. These studies open up strategies for active immunization against cancer.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:794136 HCAPLUS

DOCUMENT NUMBER: 137:309482

TITLE: Compositions for treatment of melanoma and method of

using same  
 INVENTOR(S): **Houghton, Alan N.; Bergman, Philip J.; Wolchok, Jedd D.**  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U. S. Ser. No. 627,694.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002150589	A1	20021017	US 2001-996128	20011127
WO 9825574	A2	19980618	WO 1997-US22669	19971210
WO 9825574	A3	19980903		
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6328969	B1	20011211	US 1999-308697	19990521
PRIORITY APPLN. INFO.:			US 1996-32535P	P 19961210
			US 1997-36419P	P 19970217
			WO 1997-US22669	W 19971210
			US 1999-308697	A2 19990521
			US 2000-180651P	P 20000126
			US 2000-627694	A2 20000728

AB Melanoma can be treated in a mammalian subject by administering to the subject an immunol.-effective amount of a xenogeneic melanoma-associated differentiation antigen. For example, genetic immunization with a plasmid containing a sequence encoding human gp75 has been shown to be effective in treatment of dogs with melanoma.

L15 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:194789 HCAPLUS

DOCUMENT NUMBER: 137:77424

TITLE: Strategies to overcome immune ignorance and tolerance

AUTHOR(S): Perales, Miguel-Angel; Blachere, Nathalie E.; Engelhorn, Manuel E.; Ferrone, Cristina R.; Gold, Jason S.; Gregor, Polly D.; Noffz, Gabriele; **Wolchok, Jedd D.; Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and Weill Medical School and Graduate School of Cornell University, New York, NY, 10021, USA

SOURCE: Seminars in Cancer Biology (2002), 12(1), 63-71  
 CODEN: SECBE7; ISSN: 1044-579X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Cancer poses a difficult problem for immunotherapy because it arises from the host's own tissues. A review. Many of the target antigens are tissue-specific mols. shared by cancer cells and normal cells. Thus, these are weak antigens that do not typically elicit immunity. In addition, tumors have several features that make their recognition and destruction by the immune system difficult. Despite these obstacles, several strategies for developing effective tumor immunity have been developed. Crucial to these approaches is the discovery and understanding of the mol. identity of antigens and the mechanisms involved in tumor immunity. In this review, strategies to overcome immune ignorance and tolerance are discussed. (c) 2002 Academic Press.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:824559 HCAPLUS

DOCUMENT NUMBER: 136:339051

TITLE: IL-12 and CD40 ligand DNA as molecular adjuvants for hgp100 immunization

AUTHOR(S): Ferrone, Cristina R.; Gold, Jason S.; Perales, Miguel-Angel; **Wolchok, Jedd D.**; Engelhorn, Manuel E.; Ramirez-Montagut, Teresa; **Houghton, Alan N.**

CORPORATE SOURCE: Department of Surgery, Laboratory of Tumor Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

SOURCE: Surgical Forum (2001), 52, 231-233

CODEN: SUFOAX; ISSN: 0071-8041

PUBLISHER: American College of Surgeons

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It was determined whether administration of hgp100 in combination with IL-12 or CD40 ligand can increase tumor protection, autoimmune depigmentation, or precursor T-cell frequency. The C57BL/6 mice received three weakly immunizations via gold particle bombardment by gene gun with 4 µg of plasmid DNA coding for hgp100 and 4µg of IL-12 DNA or CD40L DNA. DNA immunization with hgp100 and IL-12 or CD40L as adjuvants enhanced the immune response against syngeneic B16 melanoma cells in C57BL/6 mice. The IL-12 enhanced autoimmune depigmentation and improved tumor protection. There was uncoupling of tumor protection from autoimmune depigmentation in the case of CD40L. In spite of the improved tumor protection, CD40L caused less depigmentation than hgp100 alone.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:431795 HCAPLUS

DOCUMENT NUMBER: 134:84768

TITLE: Injection of DNA encoding granulocyte-macrophage colony-stimulating factor recruits dendritic cells for immune adjuvant effects

AUTHOR(S): Bowne, Wilbur B.; **Wolchok, Jedd D.**; Hawkins, William G.; Srinivasan, Roopa; Gregor, Polly; Blachere, Nathalie E.; Moroi, Yoichi; Engelhorn, Manuel E.; **Houghton, Alan N.**; Lewis, Jonathan J.

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Cytokines, Cellular & Molecular Therapy (1999), 5(4), 217-225

CODEN: CCMTFO; ISSN: 1368-4736

PUBLISHER: Martin Dunitz Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An important issue for effective vaccines is the development of potent adjuvants that can facilitate induction or augmentation of immunity. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a growth factor for myeloid progenitors of monocytes and dendritic cells (DC), which upon maturation are antigen-presenting cells (APC). The adjuvant effects of inoculation of DNA encoding GM-CSF into skin were studied.

Initial expts. examined whether the GM-CSF gene injected into the skin of mice could affect the d. of epidermal DC (Langerhans cells). DNA encoding GM-CSF delivered by particle bombardment into skin resulted in a significant increase of epidermal DC at the inoculation site. Kinetic anal. of epidermal recruitment after GM-CSF inoculation showed an increase in DC that peaked at seven days. This increase was accompanied by recruitment of DC into draining lymph nodes. The adjuvant effects of DNA encoding GM-CSF inoculated into skin were measured by the ability to augment antibody and T-cell responses against poorly immunogenic tumor antigens. Peptide immunization at skin sites containing epidermal DC newly recruited by GM-CSF DNA elicited T-cell responses against mutant p53, whereas peptide immunization of control skin sites did not elicit any detectable T-cell responses. Likewise, generation of antibodies following immunization with DNA encoding human gp75TRP1, a tyrosinase family member expressed by melanomas, was accelerated and protection from tumor challenge augmented by GM-CSF DNA.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:15243 HCAPLUS

DOCUMENT NUMBER: 132:333092

TITLE: Immunity by vaccination with xenogeneic tyrosinase-related protein 2 DNA requires T cells and interferon gamma: effective treatment of established tumor

AUTHOR(S): Bowne, Wilbur B.; **Wolchok, Jedd D.**; Srinivasan, Roopa; Blachere, Nathalie E.; Hawkins, William G.; Dyall, Ruben; Moroi, Yoichi; **Houghton, Alan N.**; Lewis, Jonathan J.

CORPORATE SOURCE: Departments of Surgery and Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

SOURCE: Surgical Forum (1999), 50, 299-300

CODEN: SUFOAX; ISSN: 0071-8041

PUBLISHER: American College of Surgeons

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this study was to investigate the mechanisms of immune response to xenogeneic vaccination with DNA encoding tyrosinase-related protein 2 (TRP-2) and the suppression of immune tolerance against autoimmunity and tumor growth. Mice were vaccinated using a gene gun with plasmids encoding human or murine TRP-2 and studied for autoimmunity or tumor progression. Depigmentation, lung metastasis and tumor mass were measured to quantify autoimmunity protection from tumor and tumor progression resp. The results show that depigmentation and tumor protection by this vaccine also required CD+ and CD8+ T cells, perforins and IFN- $\gamma$ . Significant regression of established tumors were also observed in mice vaccinated with human TRP-2 DNA.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:799448 HCAPLUS

DOCUMENT NUMBER: 132:92212

TITLE: Coupling and uncoupling of tumor immunity and autoimmunity

AUTHOR(S): Bowne, Wilbur B.; Srinivasan, Roopa; **Wolchok, Jedd D.**; Hawkins, William G.; Blachere, Nathalie E.; Dyall, Ruben; Lewis, Jonathan J.; **Houghton,**

**Alan N.**  
 CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY,  
 10021, USA  
 SOURCE: Journal of Experimental Medicine (1999), 190(11),  
 1717-1722  
 CODEN: JEMEAV; ISSN: 0022-1007  
 PUBLISHER: Rockefeller University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Self-antigens, in the form of differentiation antigens, are commonly recognized by the immune system on melanoma and other cancers. We have shown previously that active immunization of mice against the melanocyte differentiation antigen, a tyrosinase-related protein (TRP) gp75TRP-1 (the brown locus protein) expressed by melanomas, could induce tumor immunity and autoimmunity manifested as depigmentation. In this system, tumor immunity and autoimmunity were mediated by autoantibodies. Here, we characterize immunity against another tyrosinase family glycoprotein TRP-2 (the slaty locus protein), using the same mouse model and method of immunization. As observed previously for gp75TRP-1, immunity was induced by DNA immunization against a xenogeneic form of TRP-2, but not against the syngeneic gene, and depended on CD4+ cells. Immunization against TRP-2 induced autoantibodies and autoreactive cytotoxic T cells. In contrast to immunization against gp75TRP-1, both tumor immunity and autoimmunity required CD8+ T cells, but not antibodies. Only autoimmunity required perforin, whereas tumor immunity proceeded in the absence of perforin. Thus, immunity induced against two closely related autoantigens that are highly conserved throughout vertebrate evolution involved qual. different mechanisms, i.e., antibody vs. CD8+ T cell. However, both pathways led to tumor immunity and identical phenotypic manifestations of autoimmunity.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:613681 HCAPLUS  
 DOCUMENT NUMBER: 131:223489  
 TITLE: Use of dipeptidyl peptidase IV or fibroblast  
 activating protein- $\alpha$  for suppressing the  
 malignant phenotype of cancer cells  
 INVENTOR(S): Houghton, Alan N.; Wesley, Umadevi V.;  
 Wolchok, Jedd D.  
 PATENT ASSIGNEE(S): Sloan Kettering Institute for Cancer Research, USA  
 SOURCE: PCT Int. Appl., 69 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947152	A2	19990923	WO 1999-US5918	19990319
WO 9947152	A3	20000127		
W: AU, CA, JP, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9933572	A1	19991011	AU 1999-33572	19990319
PRIORITY APPLN. INFO.:			US 1998-78806P	P 19980320
			WO 1999-US5918	W 19990319

AB A method of suppressing the malignant phenotype or inducing apoptosis of

cancer cells in a subject comprises introducing into the cancer cell an amount of a nucleic acid encoding a dipeptidyl peptidase IV protein or fibroblast activating protein- $\alpha$ , thereby suppressing the malignant phenotype of the cancer. This invention provides a method of treating a subject with cancer which comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a purified dipeptidyl peptidase IV protein or fibroblast activating protein- $\alpha$  and a pharmaceutical acceptable carrier or diluent. This invention provides a method of inducing expression of dipeptidyl peptidase IV or fibroblast activating protein- $\alpha$  in cancer cells of a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an agent capable of activating transcription of the dipeptidyl peptidase IV gene or fibroblast activating protein- $\alpha$  and a pharmaceutical acceptable carrier or diluent.

L15 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:618239 HCAPLUS

DOCUMENT NUMBER: 129:329485

TITLE: Tumor immunity and autoimmunity induced by

immunization with homologous DNA

AUTHOR(S): Weber, Lawrence W.; Bowne, Wilbur B.; **Wolchok, Jedd D.**; Srinivasan, Roopa; Qin, Jie; Moroi, Yoichi; Clynes, Raphael; Song, Ping; Lewis, Jonathan J.; **Houghton, Alan N.**

CORPORATE SOURCE: The Swim Across America Laboratory, Sloan-Kettering Division, Cornell University Graduate School of Medical Sciences, New York, 10021, USA

SOURCE: Journal of Clinical Investigation (1998), 102(6), 1258-1264

CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The immune system can recognize self antigens expressed by cancer cells. Differentiation antigens are prototypes of these self antigens, being expressed by cancer cells and their normal cell counterparts. The tyrosinase family proteins are well characterized differentiation antigens recognized by antibodies and T cells of patients with melanoma. However, immune tolerance may prevent immunity directed against these antigens. Immunity to the brown locus protein, gp75/tyrosinase-related protein-1, was investigated in a syngeneic mouse model. C57BL/6 mice, which are tolerant to gp75, generated autoantibodies against gp75 after immunization with DNA encoding human gp75 but not syngeneic mouse gp75. Priming with human gp75 DNA broke tolerance to mouse gp75. Immunity against mouse gp75 provided significant tumor protection. Manifestations of autoimmunity were observed, characterized by coat depigmentation. Rejection of tumor challenge required CD4+ and NK1.1+ cells and Fc receptor  $\gamma$ -chain, but depigmentation did not require these components. Thus, immunization with homologous DNA broke tolerance against mouse gp75, possibly by providing help from CD4+ T cells. Mechanisms required for tumor protection were not necessary for autoimmunity, demonstrating that tumor immunity can be uncoupled from autoimmune manifestations.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:798432 HCAPLUS

DOCUMENT NUMBER: 123:311142

TITLE: Melanocyte differentiation marker gp75, the Brown

locus protein, can be regulated independently of tyrosinase and pigmentation

AUTHOR(S): Vijayasaradhi, Setaluri; Doskoch, Peter M.;  
**Wolchok, Jedd; Houghton, Alan N.**

CORPORATE SOURCE: Department Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

SOURCE: Journal of Investigative Dermatology (1995), 105(1), 113-19  
CODEN: JIDEAE; ISSN: 0022-202X

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human melanoma arises from epidermal melanocytes and displays remarkable phenotypic heterogeneity. This heterogeneity in part reflects the ability of melanoma cells to undergo differentiation along a pathway parallel to differentiation of normal melanocytes. Tyrosinase, encoded by the albino (c), and the tyrosinase-related protein-1 or gp75, encoded by the brown (b) locus, are two of the best-characterized markers for melanocyte differentiation. Both mols. are glycoproteins expressed in melanosomes, the site of pigment synthesis. The authors studied the regulation of these proteins in human melanoma cells induced by the polar-planar compound hexamethylene bisacetamide (HMBA). In well-differentiated melanoma cell lines, HMBA induced dendritic morphol. and specifically regulated the expression of melanosomal glycoproteins (but not a panel of other mols. expressed by melanoma cells). HMBA specifically down-regulated gp75 expression by rapidly decreasing the steady-state level of gp75 mRNA and gp75 synthesis. HMBA was able to down-regulate gp75 expression even in the presence of cholera toxin, which when added alone induced a two- to threefold increase in gp75 expression. In contrast to uniform down-regulation of gp75 expression, HMBA could either up-regulate or down-regulate tyrosinase expression and pigmentation. Based on the differential regulation of gp75 and tyrosinase, melanoma cells could be classified into two groups. In one group, gp75 expression was coordinately regulated with tyrosinase activity and pigmentation. In the other group, gp75 expression and tyrosinase activity and pigmentation were dissociated (with pigmentation coupling to tyrosinase activity, not to gp75 expression). These results show that in mature melanocytic cells, regulation of gp75 expression follows a pattern that can be independent of regulation of tyrosinase and pigmentation.

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L2 134 SEA FILE=HCAPLUS ABB=ON PLU=ON ("HOUGHTON ALAN"/AU OR  
"HOUGHTON ALAN N"/AU)

L3 71 SEA FILE=HCAPLUS ABB=ON PLU=ON ("BERGMAN P"/AU OR "BERGMAN P  
J"/AU)

L4 8 SEA FILE=HCAPLUS ABB=ON PLU=ON ("BERGMAN PHILIP J"/AU OR  
"BERGMAN PHILIP JOHN"/AU)

L5 33 SEA FILE=HCAPLUS ABB=ON PLU=ON ("WOLCHOK J D"/AU OR "WOLCHOK  
JEDD"/AU OR "WOLCHOK JEDD D"/AU OR "WOLCHOK JEDD DAVID"/AU)

L15 21 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (L3 OR L4 OR L5)

L17 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (L5)

L18 19 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 NOT L17

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L18 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2005:103365 HCAPLUS

DOCUMENT NUMBER: 142:296365  
 TITLE: CD8+ T-cell-dependent immunity following xenogeneic DNA immunization against CD20 in a tumor challenge model of B-cell lymphoma  
 AUTHOR(S): Palomba, Maria Lia; Roberts, Wendy K.; Dao, Tao; Manukian, Gregory; Guevara-Patino, Jose A.; **Wolchok, Jedd D.**; Scheinberg, David A.; **Houghton, Alan N.**  
 CORPORATE SOURCE: Department of Medicine and Immunology Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA  
 SOURCE: Clinical Cancer Research (2005), 11(1), 370-379  
 CODEN: CCREF4; ISSN: 1078-0432  
 PUBLISHER: American Association for Cancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The CD20 B-cell differentiation antigen is an attractive target for immunotherapy of B-cell lymphomas. In an exptl. lymphoma model, BALB/c mice were immunized with mouse or human CD20 cDNA (mCD20 and hCD20, resp.) or their extracellular domains (minigenes). IFN $\gamma$  secretion by CD8+ T cells against CD20 was detected in mice vaccinated with hCD20 or human minigene, indicating that hCD20-primed CD8+ T cells recognize syngeneic CD20. Systemic challenge with syngeneic A20 cells, an aggressive lymphoma, resulted in long-term survival in a subset of immunized mice. Overall long-term survival was 14% in groups vaccinated with the human minigene vs. 4% in control groups. CD8+ T-cell depletion during the effector phase completely abrogated this effect. Antibodies against a recombinant mouse CD20 protein produced in insect cells were detected in mice immunized with hCD20 DNA and human and mouse minigene, but not in mice receiving mCD20 DNA. These results show that active immunization with xenogeneic DNA vaccines can induce CD8+ T cell-dependent immunity against CD20.  
 REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 2004:962789 HCAPLUS  
 DOCUMENT NUMBER: 142:211646  
 TITLE: Phase II study of temozolomide plus thalidomide for the treatment of metastatic melanoma  
 AUTHOR(S): Hwu, Wen-Jen; Krown, Susan E.; Menell, Jennifer H.; Panageas, Katherine S.; Merrell, Janene; Lamb, Lynne A.; Williams, Linda J.; Quinn, Carolyn J.; Foster, Theresa; Chapman, Paul B.; Livingston, Philip O.; **Wolchok, Jedd D.**; **Houghton, Alan N.**  
 CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, USA  
 SOURCE: Journal of Clinical Oncology (2003), 21(17), 3351-3356  
 CODEN: JCONDN; ISSN: 0732-183X  
 PUBLISHER: American Society of Clinical Oncology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The aim was to further investigate the efficacy and safety of temozolomide plus thalidomide in patients with metastatic melanoma without brain metastases. Patients with histol. confirmed advanced-stage metastatic melanoma were enrolled in an open-label, phase II study. The primary end point was response rate. Patients received temozolomide (75 mg/m<sup>2</sup>/d + 6 wk with a 2-wk rest between cycles) plus concomitant thalidomide (200 mg/d with dose escalation to 400 mg/d for patients < 70 years old, or

100 mg/d with dose escalation to 250 mg/d for patients  $\geq$  70 years old). Treatment was continued until unacceptable toxicity or disease progression occurred. Thirty-eight patients (median age, 62 years) with stage IV (three patients with M1a, eight with M1b, and 26 with M1c) or stage IIIc (one patient) melanoma and a median of four metastatic sites were enrolled, and received a median of two cycles of therapy. Twelve patients (32%) had an objective tumor response, including one with an ongoing complete response of 25+ months' duration and 11 with partial responses. Five patients achieving partial response with a more than 90% reduction of disease were converted to a complete response with surgery. Treatment was generally well tolerated. Median survival was 9.5 mo (95% confidence interval, 6.05 to 19.38 mo), with a median follow-up among survivors of 24.3 mo. The combination of temozolomide plus thalidomide seems to be a promising and well-tolerated oral regimen for metastatic melanoma that merits further study.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:941945 HCAPLUS

DOCUMENT NUMBER: 142:4421

TITLE: Classification of clear-cell sarcoma as a subtype of melanoma by genomic profiling

AUTHOR(S): Segal, Neil H.; Pavlidis, Paul; Noble, William S.; Antonescu, Cristina R.; Viale, Agnes; Wesley, Umadevi V.; Busam, Klaus; Gallardo, Humilidad; DeSantis, Dianne; Brennan, Murray F.; Cordon-Cardo, Carlos; **Wolchok, Jedd D.; Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and Columbia Genome Center, Columbia University, New York, NY, USA

SOURCE: Journal of Clinical Oncology (2003), 21(9), 1775-1781  
CODEN: JCONDN; ISSN: 0732-183X

PUBLISHER: American Society of Clinical Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: To develop a genome-based classification scheme for clear-cell sarcoma (CCS), also known as melanoma of soft parts (MSP), which would have implications for diagnosis and treatment. This tumor displays characteristic features of soft tissue sarcoma (STS), including deep soft tissue primary location and a characteristic translocation, t(12;22)(q13;q12), involving EWS and ATF1 genes. CCS/MSP also has typical melanoma features, including immunoreactivity for S100 and HMB45, pigmentation, MITF-M expression, and a propensity for regional lymph node metastases. Materials and Methods: RNA samples from 21 cell lines and 60 pathol. confirmed cases of STS, melanoma, and CCS/MSP were examined using the U95A GeneChip (Affymetrix, Santa Clara, CA). Hierarchical cluster anal., principal component anal., and support vector machine (SVM) anal. exploited genomic correlations within the data to classify CCS/MSP. Results: Unsupervised analyses demonstrated a clear distinction between STS and melanoma and, furthermore, showed that CCS/MSP cluster with the melanomas as a distinct group. A supervised SVM learning approach further validated this finding and provided a user-independent approach to diagnosis. Genes of interest that discriminate CCS/MSP included those encoding melanocyte differentiation antigens, MITF, SOX10, ERBB3, and FGFR1. Conclusion: Gene expression profiles support the classification of CCS/MSP as a distinct genomic subtype of melanoma. Anal. of these gene profiles using the SVM may be an important diagnostic tool. Genomic anal. identified potential targets for the development of therapeutic strategies in the treatment of this disease.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:285012 HCAPLUS

DOCUMENT NUMBER: 141:138762

TITLE: CTLA-4 blockade in combination with xenogeneic DNA vaccines enhances T-cell responses, tumor immunity and autoimmunity to self antigens in animal and cellular model systems

AUTHOR(S): Gregor, Polly D.; **Wolchok, Jedd D.**; Ferrone, Cristina R.; Buchinshky, Heidi; Guevara-Patino, Jose A.; Perales, Miguel-Angel; Mortazavi, Fariborz; Bacich, Dean; Heston, Warren; Latouche, Jean-Baptiste; Sadelain, Michel; Allison, James P.; Scher, Howard I.; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Vaccine (2004), 22(13-14), 1700-1708

CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Xenogeneic DNA vaccination can elicit tumor immunity through T cell and antibody-dependent effector mechanisms. Blockade of CTLA-4 engagement with B7 expressed on APCs has been shown to enhance T cell-dependent immunity. We investigated whether CTLA-4 blockade could increase T-cell responses and tumor immunity elicited by DNA vaccines. CTLA-4 blockade enhanced B16 tumor rejection in mice immunized against the melanoma differentiation antigens tyrosinase-related protein 2 and gp100, and this effect was stronger when anti-CTLA-4 was administered with booster vaccinations. CTLA-4 blockade also increased the T-cell responses to prostate-specific membrane antigen (PSMA) when given with the second or third vaccination. Based on these pre-clin. studies, we suggest that anti-CTLA-4 should be tested with xenogeneic DNA vaccines against cancer and that special attention should be given to sequence and schedule of administration.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:192946 HCAPLUS

DOCUMENT NUMBER: 140:355335

TITLE: Immunity to cancer through immune recognition of altered self: studies with melanoma

AUTHOR(S): Guevara-Patino, Jose A.; Turk, Mary Jo; **Wolchok, Jedd D.**; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and the Weill Graduate School of Medical Sciences, Medical School of Cornell University, New York, NY, 10021, USA

SOURCE: Advances in Cancer Research (2003), 90, 157-177, 1 plate

CODEN: ACRSAJ; ISSN: 0065-230X

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The adaptive immune system is capable of recognizing cancer through T and B-cell receptors. However, priming adaptive immunity against self antigens is potentially a difficult task. Presentation of

altered self to the immune system is a strategy to elicit immunity against poorly immunogenic antigens. We have shown that immunization with conserved paralogues of tumor antigens can induce adaptive immunity against self antigens expressed by cancer. Remarkably, cancer immunity elicited by closely related paralogues can generate distinct adaptive immune responses, either antibody or T-cell dependent. Cancer immunity induced by xenogeneic immunization follows multiple and alternative pathways. The effector phase of tumor immunity can be mediated by cytotoxic T cells or macrophages and perhaps natural killer cells for antibody-dependent immunity. Helper CD4+ T cells are typically, but not always, required to generate immunity. Autoimmunity is frequently observed following immunization. Cancer immunity and autoimmunity use overlapping mechanisms, and therefore they are difficult to uncouple, but distinct pathways can be discerned that open the eventual possibility of uncoupling tumor immunity from autoimmunity. Studies examining the mol. basis for immunogenicity of conserved paralogues are facilitating the development of new strategies to rationally design vaccines that trigger adaptive immune responses to cancer.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:971282 HCAPLUS

DOCUMENT NUMBER: 140:26899

TITLE: Method and compositions for stimulation of an immune response to CD20 using a xenogeneic CD20 antigen

INVENTOR(S): Palomba, Maria Lia; **Houghton, Alan;**  
**Wolchok, Jedd;** Scheinberg, David A.; Roberts,  
Wendy K.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S.  
Ser. No. 627,694.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003228326	A1	20031211	US 2002-285874	20021031
WO 9825574	A2	19980618	WO 1997-US22669	19971210
WO 9825574	A3	19980903		
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6328969	B1	20011211	US 1999-308697	19990521
PRIORITY APPLN. INFO.:			US 1997-36419P	P 19970217
			US 1999-308697	A2 19970217
			WO 1997-US22669	W 19971210
			US 2000-627694	A2 20000728
			US 1996-32535P	P 19961210

AB Tolerance of the immune system for endogenous CD20 can be overcome and an immune response stimulated by administration of xenogeneic or xenoexpressed CD20 antigen. For example, mouse CD20, or antigenically-effective portions thereof, can be used to stimulate an immune response to the corresponding differentiation antigen in a human subject. Administration of xenogeneic antigens in accordance with the invention results in an effective immunity against CD20 expressed by the cancer in the treated individual, thus providing a therapeutic approach to

the treatment of lymphomas and leukemia expressing CD20. For production of a recombinant mouse CD20 fusion protein (recCD20) the inventors used the baculovirus expression system to obtain a partially purified recCD20 for the use as xenoexpressed CD20.

L18 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 2003:690210 HCAPLUS  
 DOCUMENT NUMBER: 139:306210  
 TITLE: GM-CSF DNA induces specific patterns of cytokines and chemokines in the skin: implications for DNA vaccines  
 AUTHOR(S): Perales, Miguel-Angel; Fantuzzi, Giamila; Goldberg, Stacie M.; Turk, Mary Jo; Mortazavi, Fariborz; Busam, Klaus; **Houghton, Alan N.**; Dinarello, Charles A.; **Wolchok, Jedd D.**  
 CORPORATE SOURCE: The Swim Across America Laboratory, Memorial Sloan-Kettering Cancer Center and Weill Graduate School of Medical Sciences of Cornell University, New York, USA  
 SOURCE: Cytokines, Cellular & Molecular Therapy (2002), 7(3), 125-133  
 CODEN: CCMTFO; ISSN: 1368-4736  
 PUBLISHER: Taylor & Francis Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances immune responses by inducing the proliferation, maturation, and migration of dendritic cells, and the expansion and differentiation of B and T lymphocytes. Similar biol. effects have been observed with the use of GM-CSF DNA in mouse models for therapy of cancer and infectious diseases, and its use is currently being investigated in clin. trials in combination with DNA vaccines. To further understand the adjuvant mechanisms of GM-CSF DNA, we examined early events following its administration. We found measurable levels of GM-CSF protein in the skin and muscle, as well as in serum. Measurements of other cytokine and chemokine levels revealed differential expression patterns over time. The early response was characterized by high levels of inflammatory mols., including IL-1 $\beta$ , IL-6, TNF $\alpha$ , RANTES, MIP-1 $\alpha$  and MCP-1, later followed by expression of precursor Th1 cytokines, IL-12 and IL-18, concomitant with IFN $\gamma$  production. Local production of GM-CSF protein also resulted in the early recruitment of polymorphonuclear cells and later recruitment of mononuclear cells, including dendritic cells. These results have implications for understanding early events in the immune response to DNA vaccines, and provide a basis for development of new approaches to cancer vaccines, including the use of cytokine genes as adjuvants.  
 REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 2003:429991 HCAPLUS  
 DOCUMENT NUMBER: 139:163255  
 TITLE: Immunity to melanoma: unraveling the relation of tumor immunity and autoimmunity  
 AUTHOR(S): Ramirez-Montagut, Teresa; Turk, Mary Jo; **Wolchok, Jedd D.**; Guevara-Patino, Jose A.; **Houghton, Alan N.**  
 CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, Weill Graduate School of Medical Sciences of Cornell University, New York, NY, 10021, USA  
 SOURCE: Oncogene (2003), 22(20), 3180-3187

PUBLISHER: CODEN: ONCNES; ISSN: 0950-9232  
 Nature Publishing Group  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English

AB A review. Cancer cells express self-antigens that are weakly recognized by the immune system. Even though responses against autologous cells are difficult to induce, the immune system is still able to mount a response against cancer. The discovery of the mol. identity of antigens that are recognized by the immune system of melanoma patients has led to the elucidation of tumor immunity at a cellular and mol. level. Multiple pathways in both the priming and effector phases of melanoma rejection have been described. Animal models' active immunotherapies for melanoma show a requirement for the cellular compartment of the immune system in the priming phase, primarily CD4+ T cells. More diverse elements are required for the effector phase, including components from the innate immune system (macrophages, complement and/or natural killer cells) and from the adaptive immune system (CD8+ T cells and B cells). Minor differences in amino-acid sequences of antigens must determine the particular mechanisms involved in tumor rejection. Since the immune system contains T and B cells that recognize and reject autologous cells, a consequence of tumor immunity is potential autoimmunity. There are distinct pathways for tumor immunity and autoimmunity. The requirements for autoimmunity at the priming phase seem to be CD4+/IFN- $\gamma$  dependent while the effector mechanisms are alternative and redundant. Vitiligo (autoimmune hypopigmentation) can be mediated by T cells, Fc $\gamma$ R+ macrophages and/or complement.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STM

ACCESSION NUMBER: 2003:345937 HCAPLUS

DOCUMENT NUMBER: 139:34865

TITLE: A Single Heteroclitic Epitope Determines Cancer Immunity After Xenogeneic DNA Immunization Against a Tumor Differentiation Antigen

AUTHOR(S): Gold, Jason S.; Ferrone, Cristina R.; Guevara-Patino, Jose A.; Hawkins, William G.; Dyall, Ruben; Engelhorn, Manuel E.; Wolchok, Jedd D.; Lewis, Jonathan J.; Houghton, Alan N.

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, Cornell University, New York, NY, 10021, USA

SOURCE: Journal of Immunology (2003), 170(10), 5188-5194  
 CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Successful active immunization against cancer requires induction of immunity against self or mutated self Ags. However, immunization against self Ags is difficult. Xenogeneic immunization with orthologous Ags induces cancer immunity. The present study evaluated the basis for immunity induced by active immunization against a melanoma differentiation Ag, gp100. Tumor rejection of melanoma was assessed after immunization with human gp100 (hgp100) DNA compared with mouse gp100 (mgp100). C57BL/6 mice immunized with xenogeneic full-length hgp100 DNA were protected against syngeneic melanoma challenge. In contrast, mice immunized with hgp100 DNA and given i.p. tolerizing doses of the hgp100 Db-restricted peptide, hgp10025-33, were incapable of rejecting tumors. Furthermore, mice immunized with DNA constructs of hgp100 in which the hgp10025-27 epitope was substituted with the weaker Db-binding epitope from mgp100

(mgp10025-27) or a mutated epitope unable to bind Db did not reject B16 melanoma. Mice immunized with a minigene construct of hgp10025-33 rejected B16 melanoma, whereas mice immunized with the mgp10025-33 minigene did not develop protective tumor immunity. In this model of xenogeneic DNA immunization, the presence of an hgp100 heteroclitic epitope with a higher affinity for MHC created by three amino acid (25 to 27) substitutions at predicted minor anchor residues was necessary and sufficient to induce protective tumor immunity in H-2b mice with melanoma.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:166483 HCAPLUS

DOCUMENT NUMBER: 138:336082

TITLE: The role of lipopolysaccharide in T-cell responses following DNA vaccination

AUTHOR(S): Hawkins, William G.; Trcka, Jiri; Segal, Neil; Blachere, Nathalie E.; Gold, Jason S.; Moroi, Yoichi; Bowne, Wilbur B.; Lewis, Jonathan J.; **Wolchok, Jedd D.; Houghton, Alan N.**

CORPORATE SOURCE: Swim Across America Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Vaccine (2003), 21(13-14), 1548-1553

CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Bacterial products, including lipopolysaccharide (LPS), are potential impurities in plasmid DNA vaccines. LPS has immunostimulatory properties even at exceedingly low concns. through activation of Toll-like receptor 4 (TLR4). The potency of T-cell responses after vaccination was tested with DNA containing high LPS or depleted of LPS in TLR4-competent and TLR4-deficient mice. CD8+ T-cell responses were readily induced in TLR4-deficient mice immunized with DNA depleted of LPS. LPS in DNA vaccines is not required for CD8+ T-cell responses.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:967908 HCAPLUS

DOCUMENT NUMBER: 138:151745

TITLE: Multiple pathways to tumor immunity and concomitant autoimmunity

AUTHOR(S): Turk, Mary Jo; **Wolchok, Jedd D.**; Guevara-Patino, Jose A.; Goldberg, Stacie M.; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and the Weill Graduate School of Medical Sciences of Cornell University, New York, NY, USA

SOURCE: Immunological Reviews (2002), 188, 122-135

CODEN: IMRED2; ISSN: 0105-2896

PUBLISHER: Blackwell Munksgaard

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The immune repertoire contains T cells and B cells that can recognize autologous cancer cells. This repertoire is directed against self, and in some cases altered self (mutations). Priming immune responses against self antigens can be difficult. Strategies are

presented using altered self to elicit immunity against self in poorly immunogenic tumor models. Mechanisms underlying immunity to self antigens on cancer cells show that the immune system can use diverse strategies for cancer immunity, in both the immunization and the effector phases. CD4+ T cells are typically, but not always, required for immunization. The effector phase of tumor immunity can involve cytotoxic T cells, macrophages with activating Fc receptors, and/or killer domain mols. This diversity in the effector phase is observed even when immunizing with conserved paralogs. A consequence of tumor immunity is potentially autoimmunity, which may be undesirable. Autoimmunity uses similar mechanisms as tumor immunity, but tumor immunity and autoimmunity can uncouple. These studies open up strategies for active immunization against cancer.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:194789 HCAPLUS

DOCUMENT NUMBER: 137:77424

TITLE: Strategies to overcome immune ignorance and tolerance

AUTHOR(S): Perales, Miguel-Angel; Blachere, Nathalie E.; Engelhorn, Manuel E.; Ferrone, Cristina R.; Gold, Jason S.; Gregor, Polly D.; Noffz, Gabriele; **Wolchok, Jedd D.; Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center and Weill Medical School and Graduate School of Cornell University, New York, NY, 10021, USA

SOURCE: Seminars in Cancer Biology (2002), 12(1), 63-71  
CODEN: SECBE7; ISSN: 1044-579X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Cancer poses a difficult problem for immunotherapy because it arises from the host's own tissues. A review. Many of the target antigens are tissue-specific mols. shared by cancer cells and normal cells. Thus, these are weak antigens that do not typically elicit immunity. In addition, tumors have several features that make their recognition and destruction by the immune system difficult. Despite these obstacles, several strategies for developing effective tumor immunity have been developed. Crucial to these approaches is the discovery and understanding of the mol. identity of antigens and the mechanisms involved in tumor immunity. In this review, strategies to overcome immune ignorance and tolerance are discussed. (c) 2002 Academic Press.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:824559 HCAPLUS

DOCUMENT NUMBER: 136:339051

TITLE: IL-12 and CD40 ligand DNA as molecular adjuvants for hgp100 immunization

AUTHOR(S): Ferrone, Cristina R.; Gold, Jason S.; Perales, Miguel-Angel; **Wolchok, Jedd D.**; Engelhorn, Manuel E.; Ramirez-Montagut, Teresa; **Houghton, Alan N.**

CORPORATE SOURCE: Department of Surgery, Laboratory of Tumor Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

SOURCE: Surgical Forum (2001), 52, 231-233

CODEN: SUFOAX; ISSN: 0071-8041  
 PUBLISHER: American College of Surgeons  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB It was determined whether administration of hgp100 in combination with IL-12 or CD40 ligand can increase tumor protection, autoimmune depigmentation, or precursor T-cell frequency. The C57BL/6 mice received three weakly immunizations via gold particle bombardment by gene gun with 4 µg of plasmid DNA coding for hgp100 and 4µg of IL-12 DNA or CD40L DNA. DNA immunization with hgp100 and IL-12 or CD40L as adjuvants enhanced the immune response against syngeneic B16 melanoma cells in C57BL/6 mice. The IL-12 enhanced autoimmune depigmentation and improved tumor protection. There was uncoupling of tumor protection from autoimmune depigmentation in the case of CD40L. In spite of the improved tumor protection, CD40L caused less depigmentation than hgp100 alone.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:431795 HCAPLUS

DOCUMENT NUMBER: 134:84768

TITLE: Injection of DNA encoding granulocyte-macrophage colony-stimulating factor recruits dendritic cells for immune adjuvant effects

AUTHOR(S): Bowne, Wilbur B.; **Wolchok, Jedd D.**; Hawkins, William G.; Srinivasan, Roopa; Gregor, Polly; Blachere, Nathalie E.; Moroi, Yoichi; Engelhorn, Manuel E.; **Houghton, Alan N.**; Lewis, Jonathan J.

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Cytokines, Cellular & Molecular Therapy (1999), 5(4), 217-225

CODEN: CCMTFO; ISSN: 1368-4736

PUBLISHER: Martin Dunitz Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An important issue for effective vaccines is the development of potent adjuvants that can facilitate induction or augmentation of immunity. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a growth factor for myeloid progenitors of monocytes and dendritic cells (DC), which upon maturation are antigen-presenting cells (APC). The adjuvant effects of inoculation of DNA encoding GM-CSF into skin were studied. Initial expts. examined whether the GM-CSF gene injected into the skin of mice could affect the d. of epidermal DC (Langerhans cells). DNA encoding GM-CSF delivered by particle bombardment into skin resulted in a significant increase of epidermal DC at the inoculation site. Kinetic anal. of epidermal recruitment after GM-CSF inoculation showed an increase in DC that peaked at seven days. This increase was accompanied by recruitment of DC into draining lymph nodes. The adjuvant effects of DNA encoding GM-CSF inoculated into skin were measured by the ability to augment antibody and T-cell responses against poorly immunogenic tumor antigens. Peptide immunization at skin sites containing epidermal DC newly recruited by GM-CSF DNA elicited T-cell responses against mutant p53, whereas peptide immunization of control skin sites did not elicit any detectable T-cell responses. Likewise, generation of antibodies following immunization with DNA encoding human gp75TRP1, a tyrosinase family member expressed by melanomas, was accelerated and protection from tumor challenge augmented by GM-CSF DNA.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:15243 HCAPLUS

DOCUMENT NUMBER: 132:333092

TITLE: Immunity by vaccination with xenogeneic tyrosinase-related protein 2 DNA requires T cells and interferon gamma: effective treatment of established tumor

AUTHOR(S): Bowne, Wilbur B.; **Wolchok, Jedd D.**; Srinivasan, Roopa; Blachere, Nathalie E.; Hawkins, William G.; Dyall, Ruben; Moroi, Yoichi; **Houghton, Alan N.**; Lewis, Jonathan J.

CORPORATE SOURCE: Departments of Surgery and Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

SOURCE: Surgical Forum (1999), 50, 299-300

CODEN: SUFOAX; ISSN: 0071-8041

PUBLISHER: American College of Surgeons

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this study was to investigate the mechanisms of immune response to xenogeneic vaccination with DNA encoding tyrosinase-related protein 2 (TRP-2) and the suppression of immune tolerance against autoimmunity and tumor growth. Mice were vaccinated using a gene gun with plasmids encoding human or murine TRP-2 and studied for autoimmunity or tumor progression. Depigmentation, lung metastasis and tumor mass were measured to quantify autoimmunity protection from tumor and tumor progression resp. The results show that depigmentation and tumor protection by this vaccine also required CD4+ and CD8+ T cells, perforins and IFN- $\gamma$ . Significant regression of established tumors were also observed in mice vaccinated with human TRP-2 DNA.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:799448 HCAPLUS

DOCUMENT NUMBER: 132:92212

TITLE: Coupling and uncoupling of tumor immunity and autoimmunity

AUTHOR(S): Bowne, Wilbur B.; Srinivasan, Roopa; **Wolchok, Jedd D.**; Hawkins, William G.; Blachere, Nathalie E.; Dyall, Ruben; Lewis, Jonathan J.; **Houghton, Alan N.**

CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA

SOURCE: Journal of Experimental Medicine (1999), 190(11), 1717-1722

CODEN: JEMEAV; ISSN: 0022-1007

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Self-antigens, in the form of differentiation antigens, are commonly recognized by the immune system on melanoma and other cancers. We have shown previously that active immunization of mice against the melanocyte differentiation antigen, a tyrosinase-related protein (TRP) gp75TRP-1 (the brown locus protein) expressed by melanomas, could induce tumor immunity and autoimmunity manifested as depigmentation. In this system, tumor immunity and autoimmunity were mediated by autoantibodies. Here, we

characterize immunity against another tyrosinase family glycoprotein TRP-2 (the slaty locus protein), using the same mouse model and method of immunization. As observed previously for gp75TRP-1, immunity was induced by DNA immunization against a xenogeneic form of TRP-2, but not against the syngeneic gene, and depended on CD4+ cells. Immunization against TRP-2 induced autoantibodies and autoreactive cytotoxic T cells. In contrast to immunization against gp75TRP-1, both tumor immunity and autoimmunity required CD8+ T cells, but not antibodies. Only autoimmunity required perforin, whereas tumor immunity proceeded in the absence of perforin. Thus, immunity induced against two closely related autoantigens that are highly conserved throughout vertebrate evolution involved qual. different mechanisms, i.e., antibody vs. CD8+ T cell. However, both pathways led to tumor immunity and identical phenotypic manifestations of autoimmunity.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:613681 HCAPLUS

DOCUMENT NUMBER: 131:223489

TITLE: Use of dipeptidyl peptidase IV or fibroblast activating protein- $\alpha$  for suppressing the malignant phenotype of cancer cells

INVENTOR(S): Houghton, Alan N.; Wesley, Umadevi V.; Wolchok, Jedd D.

PATENT ASSIGNEE(S): Sloan Kettering Institute for Cancer Research, USA

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947152	A2	19990923	WO 1999-US5918	19990319
WO 9947152	A3	20000127		
W: AU, CA, JP, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9933572	A1	19991011	AU 1999-33572	19990319
PRIORITY APPLN. INFO.:			US 1998-78806P	P 19980320
			WO 1999-US5918	W 19990319

AB A method of suppressing the malignant phenotype or inducing apoptosis of cancer cells in a subject comprises introducing into the cancer cell an amount of a nucleic acid encoding a dipeptidyl peptidase IV protein or fibroblast activating protein- $\alpha$ , thereby suppressing the malignant phenotype of the cancer. This invention provides a method of treating a subject with cancer which comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a purified dipeptidyl peptidase IV protein or fibroblast activating protein- $\alpha$  and a pharmaceutical acceptable carrier or diluent. This invention provides a method of inducing expression of dipeptidyl peptidase IV or fibroblast activating protein- $\alpha$  in cancer cells of a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an agent capable of activating transcription of the dipeptidyl peptidase IV gene or fibroblast activating protein- $\alpha$  and a pharmaceutical acceptable carrier or diluent.

L18 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:618239 HCAPLUS  
 DOCUMENT NUMBER: 129:329485  
 TITLE: Tumor immunity and autoimmunity induced by immunization with homologous DNA  
 AUTHOR(S): Weber, Lawrence W.; Bowne, Wilbur B.; **Wolchok, Jedd D.**; Srinivasan, Roopa; Qin, Jie; Moroi, Yoichi; Clynes, Raphael; Song, Ping; Lewis, Jonathan J.; **Houghton, Alan N.**  
 CORPORATE SOURCE: The Swim Across America Laboratory, Sloan-Kettering Division, Cornell University Graduate School of Medical Sciences, New York, 10021, USA  
 SOURCE: Journal of Clinical Investigation (1998), 102(6), 1258-1264  
 CODEN: JCINAO; ISSN: 0021-9738  
 PUBLISHER: Rockefeller University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The immune system can recognize self antigens expressed by cancer cells. Differentiation antigens are prototypes of these self antigens, being expressed by cancer cells and their normal cell counterparts. The tyrosinase family proteins are well characterized differentiation antigens recognized by antibodies and T cells of patients with melanoma. However, immune tolerance may prevent immunity directed against these antigens. Immunity to the brown locus protein, gp75/tyrosinase-related protein-1, was investigated in a syngeneic mouse model. C57BL/6 mice, which are tolerant to gp75, generated autoantibodies against gp75 after immunization with DNA encoding human gp75 but not syngeneic mouse gp75. Priming with human gp75 DNA broke tolerance to mouse gp75. Immunity against mouse gp75 provided significant tumor protection. Manifestations of autoimmunity were observed, characterized by coat depigmentation. Rejection of tumor challenge required CD4+ and NK1.1+ cells and Fc receptor  $\gamma$ -chain, but depigmentation did not require these components. Thus, immunization with homologous DNA broke tolerance against mouse gp75, possibly by providing help from CD4+ T cells. Mechanisms required for tumor protection were not necessary for autoimmunity, demonstrating that tumor immunity can be uncoupled from autoimmune manifestations.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:798432 HCAPLUS  
 DOCUMENT NUMBER: 123:311142  
 TITLE: Melanocyte differentiation marker gp75, the Brown locus protein, can be regulated independently of tyrosinase and pigmentation  
 AUTHOR(S): Vijayasaradhi, Setaluri; Doskoch, Peter M.; **Wolchok, Jedd; Houghton, Alan N.**  
 CORPORATE SOURCE: Department Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA  
 SOURCE: Journal of Investigative Dermatology (1995), 105(1), 113-19  
 CODEN: JIDEAE; ISSN: 0022-202X  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Human melanoma arises from epidermal melanocytes and displays remarkable phenotypic heterogeneity. This heterogeneity in part reflects the ability of melanoma cells to undergo differentiation along a pathway parallel to differentiation of normal melanocytes. Tyrosinase, encoded by the albino

(c), and the tyrosinase-related protein-1 or gp75, encoded by the brown (b) locus, are two of the best-characterized markers for melanocyte differentiation. Both mols. are glycoproteins expressed in melanosomes, the site of pigment synthesis. The authors studied the regulation of these proteins in human melanoma cells induced by the polar-planar compound hexamethylene bisacetamide (HMBA). In well-differentiated melanoma cell lines, HMBA induced dendritic morphol. and specifically regulated the expression of melanosomal glycoproteins (but not a panel of other mols. expressed by melanoma cells). HMBA specifically down-regulated gp75 expression by rapidly decreasing the steady-state level of gp75 mRNA and gp75 synthesis. HMBA was able to down-regulate gp75 expression even in the presence of cholera toxin, which when added alone induced a two- to threefold increase in gp75 expression. In contrast to uniform down-regulation of gp75 expression, HMBA could either up-regulate or down-regulate tyrosinase expression and pigmentation. Based on the differential regulation of gp75 and tyrosinase, melanoma cells could be classified into two groups. In one group, gp75 expression was coordinately regulated with tyrosinase activity and pigmentation. In the other group, gp75 expression and tyrosinase activity and pigmentation were dissociated (with pigmentation coupling to tyrosinase activity, not to gp75 expression). These results show that in mature melanocytic cells, regulation of gp75 expression follows a pattern that can be independent of regulation of tyrosinase and pigmentation.

=> => file biosis, medline, embase

FILE 'BIOSIS' ENTERED AT 15:19:36 ON 12 APR 2005

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FILE 'MEDLINE' ENTERED AT 15:19:36 ON 12 APR 2005

FILE 'EMBASE' ENTERED AT 15:19:36 ON 12 APR 2005

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=> d stat que

L25 13005 SEA TYROSINASE?  
 L26 11131 SEA XENOGEN?  
 L27 164862 SEA MELANOMA?  
 L28 27 SEA L25 AND L26 AND L27  
 L29 13 DUP REM L28 (14 DUPLICATES REMOVED)

=> d ibib abs l29 tot

L29 ANSWER 1 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 DUPLICATE 1

ACCESSION NUMBER: 2004:311588 BIOSIS

DOCUMENT NUMBER: PREV200400311408

TITLE: CTLA-4 blockade in combination with **xenogeneic**  
 DNA vaccines enhances T-cell responses, tumor immunity and  
 autoimmunity to self antigens in animal and cellular model  
 systems.

AUTHOR(S): Gregor, Polly D. [Reprint Author]; Wolchok, Jedd D.;  
 Ferrone, Cristina R.; Buchinshky, Heidi; Guevara-Patino,  
 Jose A.; Perales, Miguel-Angel; Mortazavi, Fariborz;  
 Bachich, Dean; Heston, Warren; Latouche, Jean-Baptiste;  
 Sadelain, Michel; Allison, James P.; Scher, Howard I.;  
 Houghton, Alan N.

CORPORATE SOURCE: Mem Sloan Kettering Canc Ctr, 1275 York Ave, New York, NY,

10021, USA  
 gregorp@mskcc.org  
 SOURCE: Vaccine, (April 16 2004) Vol. 22, No. 13-14, pp. 1700-1708.  
 print.  
 ISSN: 0264-410X (ISSN print).  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 15 Jul 2004  
 Last Updated on STN: 15 Jul 2004

AB **Xenogeneic** DNA vaccination can elicit tumor immunity through T cell and antibody-dependent effector mechanisms. Blockade of CTLA-4 engagement with B7 expressed on APCs has been shown to enhance T cell-dependent immunity. We investigated whether CTLA-4 blockade could increase T-cell responses and tumor immunity elicited by DNA vaccines. CTLA-4 blockade enhanced B 16 tumor rejection in mice immunized against the **melanoma** differentiation antigens **tyrosinase**-related protein 2 and gp100, and this effect was stronger when anti-CTLA-4 was administered with booster vaccinations. CTLA-4 blockade also increased the T-cell responses to prostate-specific membrane antigen (PSMA) when given with the second or third vaccination. Based on these pre-clinical studies, we suggest that anti-CTLA-4 should be tested with **xenogeneic** DNA vaccines against cancer and that special attention should be given to sequence and schedule of administration. Copyright 2004 Elsevier Ltd. All rights reserved.

L29 ANSWER 2 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 DUPLICATE 2

ACCESSION NUMBER: 2004:227081 BIOSIS  
 DOCUMENT NUMBER: PREV200400227766  
 TITLE: Partial **tyrosinase**-specific self tolerance by  
 HLA-A\*0201-restricted cytotoxic T lymphocytes in mice and  
 man.  
 AUTHOR(S): Lotz, Carina; Ferreira, Edite Antunes; Drexler, Ingo;  
 Mutallib, Sarah Abdel; Huber, Christoph; Sutter, Gerd;  
 Theobald, Matthias [Reprint Author]  
 CORPORATE SOURCE: Department of Hematology and Oncology, Johannes  
 Gutenberg-University, Langenbeckstr. 1, Mainz, 55101,  
 Germany  
 m.theobald@3-med.klinik.uni-mainz.de  
 SOURCE: International Journal of Cancer, (10 February 2004) Vol.  
 108, No. 4, pp. 571-579. print.  
 CODEN: IJCNAA. ISSN: 0020-7136.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 28 Apr 2004  
 Last Updated on STN: 28 Apr 2004

AB The human **tyrosinase** (hTyr) (369-377) cytotoxic T lymphocyte (CTL) epitope is presented by malignant **melanoma** and various nontransformed cells in association with human leukocyte antigen (HLA)-A\*0201 (A2.1) and used for vaccination-based immunotherapy of **melanoma** patients. Its mouse homologue, mTyr (369-377), is naturally processed and bound by A2.1 with equivalent efficacy and thus enabled us to explore the effect of self tolerance on Tyr-specific T cells in different lines of A2.1 transgenic (Tg) mice and man. We found that self Tyr-reactive CTL in Tg mice and, importantly, in man were affected by partial tolerance resulting in only residual T lymphocytes of higher avidity for self Tyr along with low-avidity T cells to be present in the periphery. Immunizing mice with the **xenogeneic** nonself Tyr peptide facilitated the generation of self Tyr-reactive CTL. As compared

to Tyr-reactive CTL induced by high amounts of the self Tyr epitope, however, the nonself antigen (Ag) had no effect on improving the avidity of self Tyr-specific mouse and human T cells. Depleting mice of CD25+ T cells with and without CTL-associated Ag 4 (CTLA-4) blockade demonstrated that tolerance of Tyr-specific CTL was not regulated by CD4+CD25+ T regulatory cells (Treg) or CTLA-4. Our studies have important implications for the design of anti-Tyr-based immunotherapeutics.

L29 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 3  
 ACCESSION NUMBER: 2003174788 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12684396  
 TITLE: Long-term survival of dogs with advanced malignant **melanoma** after DNA vaccination with **xenogeneic** human **tyrosinase**: a phase I trial.  
 AUTHOR: Bergman Philip J; McKnight Joanne; Novosad Andrew; Charney Sarah; Farrelly John; Craft Diane; Wulderk Michelle; Jeffers Yusuf; Sadelain Michel; Hohenhaus Ann E; Segal Neil; Gregor Polly; Engelhorn Manuel; Riviere Isabelle; Houghton Alan N; Wolchok Jedd D  
 CORPORATE SOURCE: Donaldson-Atwood Cancer Clinic and Flaherty Comparative Oncology Laboratory, The E&M Bobst Hospital of the Animal Medical Center, New York, New York 10021, USA..  
 Philip.bergman@amcnyc.org  
 CONTRACT NUMBER: P01 CA33049 (NCI)  
 P01 CA59350 (NCI)  
 R01 CA56821 (NCI)  
 SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2003 Apr) 9 (4) 1284-90.  
 Journal code: 9502500. ISSN: 1078-0432.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: (CLINICAL TRIAL)  
 (CLINICAL TRIAL, PHASE I)  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200401  
 ENTRY DATE: Entered STN: 20030417  
 Last Updated on STN: 20040121  
 Entered Medline: 20040120  
 AB PURPOSE: Canine malignant **melanoma** (CMM) is a spontaneous, aggressive, and metastatic neoplasm. Preclinical mouse studies have shown that **xenogeneic** DNA vaccination with genes encoding **tyrosinase** family members can induce antibody and cytotoxic T-cell responses, resulting in tumor rejection. These studies provided the rationale for a trial of **xenogeneic** DNA vaccination in CMM using the human **tyrosinase** gene. EXPERIMENTAL DESIGN: Three cohorts of three dogs each with advanced (WHO stage II, III, or IV) CMM received four biweekly i.m. injections (dose levels 100, 500, or 1500 micro g, respectively/vaccination) of human **tyrosinase** plasmid DNA i.m. via the Biojector2000 delivery device. RESULTS: Mild local reactions at injection sites were the only toxicities observed, with no signs of autoimmunity. One dog with stage IV disease had a complete clinical response in multiple lung metastases for 329 days. Two dogs with stage IV disease had long-term survivals (421 and 588+ days) in the face of significant bulky metastatic disease, and two other dogs with locally controlled stage II/III disease had long-term survivals (501 and 496 days) with no evidence of **melanoma** on necropsy. Four other dogs were

euthanized because of progression of the primary tumor. The Kaplan-Meier median survival time for all nine dogs was 389 days. CONCLUSIONS: The results of this trial demonstrate that **xenogeneic** DNA vaccination of dogs with advanced malignant **melanoma** is a safe and potentially therapeutic modality. On the basis of these results, additional evaluation of this novel therapeutic is warranted in locally controlled CMM and advanced human **melanoma**.

L29 ANSWER 4 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 ACCESSION NUMBER: 2003:513728 BIOSIS  
 DOCUMENT NUMBER: PREV200300513108  
 TITLE: Phase I trials of **xenogeneic** DNA vaccination with human **tyrosinase** or murine gp75 in client-owned dogs with advanced stage spontaneous malignant **melanoma**.  
 AUTHOR(S): Bergman, Philip J. [Reprint Author]; McKnight, Joanne [Reprint Author]; Houghton, Alan N.; Dowd, Michael [Reprint Author]; Craft, Diane M.; Kang, Xiaoqiang; Riviere, Isabelle; Hohenhaus, Ann E.; Hicklin, Daniel J.; Wolchok, Jedd  
 CORPORATE SOURCE: The Animal Medical Center, New York, NY, USA  
 SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 758. print.  
 Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.  
 ISSN: 0197-016X.  
 DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 5 Nov 2003  
 Last Updated on STN: 5 Nov 2003

L29 ANSWER 5 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.  
 on STN  
 ACCESSION NUMBER: 2002314339 EMBASE  
 TITLE: **Xenogeneic** DNA immunization in **melanoma** models for minimal residual disease.  
 AUTHOR: Hawkins W.G.; Gold J.S.; Blachere N.E.; Bowne W.B.; Hoos A.; Lewis J.J.; Houghton A.N.  
 CORPORATE SOURCE: Dr. W.G. Hawkins, Swim Across America Laboratory, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, United States  
 SOURCE: Journal of Surgical Research, (2002) Vol. 102, No. 2, pp. 137-143.  
 Refs: 10  
 ISSN: 0022-4804 CODEN: JSGRA2  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 009 Surgery  
 016 Cancer  
 026 Immunology, Serology and Transplantation  
 030 Pharmacology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 20020919  
 Last Updated on STN: 20020919  
 AB Introduction. DNA immunization with **xenogeneic** genes encoding

homologous antigens protects mice against tumor challenge with syngeneic **melanoma** in a lung metastasis model. The effect of **xenogeneic** human TRP-2 (hTRP2) DNA immunization on disease confined to an orthotopic site, the skin, and in a model of minimal residual disease that is relevant to a setting of adjuvant therapy for micrometastatic cancer is reported. Methods. Immunization and tumor challenge with Bl6F10LM3 **melanoma** were performed in C57BL/6 mice and in mice genetically deficient in MHC class I or II molecules. A **melanoma** variant of Bl6 with a predilection for lung metastasis was selected and used to challenge C57BL/6 mice. Tumor challenge in the footpad with the Bl6 variant was followed by local tumor growth and lung metastasis. The tumor-bearing distal extremities were surgically resected and mice were randomized to receive hTRP2 DNA immunization or no treatment. Approximately 3-5 weeks after surgical resection, lungs were harvested and metastases counted. Results. **Xenogeneic** DNA immunization with hTRP2 prevented tumor growth in the skin by a mechanism requiring CD4(+) and CD8(+) T cells but did not inhibit the growth of established tumors. Adjuvant immunization with hTRP2 DNA after resection significantly reduced lung metastases and decreased local recurrence rates after surgical resection. Conclusions. **Xenogeneic** DNA immunization with hTRP2 was effective in protecting mice from intradermal tumor challenge. Immunization prevented local recurrence and the development of metastases in a mouse model of minimal residual disease, supporting a role for DNA immunization against melanosomal antigens as an adjuvant to surgery in high-risk primary **melanomas**. .COPYRG.T.  
2001 Elsevier Science.

L29 ANSWER 6 OF 13 MEDLINE on STN  
 ACCESSION NUMBER: 2003226467 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12747770  
 TITLE: Alternative roles for interferon-gamma in the immune response to DNA vaccines encoding related melanosomal antigens.  
 AUTHOR: Wolchok J D; Srinivasan R; Perales M A; Houghton A N; Bowne W B; Blachere N E  
 CORPORATE SOURCE: The Swim Across America Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.. wolchokj@mskcc.org  
 CONTRACT NUMBER: CA09207 (NCI)  
 CA09512 (NCI)  
 K12CA01712 (NCI)  
 SOURCE: Cancer immunity [electronic resource] : a journal of the Academy of Cancer Immunology, (2001 Aug 16) 1 9. Electronic Publication: 2001-08-16. Journal code: 101119871. ISSN: 1424-9634.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200306  
 ENTRY DATE: Entered STN: 20030516  
 Last Updated on STN: 20030608  
 Entered Medline: 20030606  
 AB **Tyrosinase**-related proteins-1 and -2 (gp75/TRP-1 and TRP-2) are melanosomal membrane glycoproteins recognized by antibodies and T-cells from patients with **melanoma**. **Xenogeneic** DNA immunization against gp75/TRP-1 generates antibody-dependent tumor immunity and autoimmune depigmentation. In contrast **xenogeneic** TRP-2 DNA immunization induces immunity mediated by CD8+ T-cells. The

role of IFN-gamma in the generation of tumor immunity and autoimmune depigmentation in these two models was investigated. No tumor protection and minimal depigmentation was observed after immunization with human TRP-2 DNA in mice deficient in IFN-gamma ligand. Repletion with recombinant murine IFN-gamma restored tumor immunity. Experiments using IL4 deficient mice demonstrated that tumor immunity was unaffected but that autoimmune depigmentation was potentially accelerated, consistent with down-modulation of autoimmunity against TRP-2 by IL4. In contrast, IFN-gamma was not required for the generation of immunity to gp75/TRP-1. In fact, exogenous IFN-gamma ablated autoantibody responses against gp75/TRP-1 after **xenogeneic** DNA immunization, consistent with a down-regulatory effect of IFN-gamma. These results show that immunity to TRP-2 following DNA immunization uses an IFN-gamma-dependent Th1 pathway, but immunity to gp75/TRP-1 is down-regulated by IFN-gamma.

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DUPLICATE 4

ACCESSION NUMBER: 2001:69212 BIOSIS

DOCUMENT NUMBER: PREV200100069212

TITLE: Dendritic cells break tolerance and induce protective immunity against a melanocyte differentiation antigen in an autologous **melanoma** model.

AUTHOR(S): Schreurs, Marco W. J.; Eggert, Andreas A. O.; de Boer, Annemiek J.; Vissers, Joost L. M.; van Hall, Thorbald; Offringa, Rienk; Figdor, Carl G.; Adema, Gosse J. [Reprint author]

CORPORATE SOURCE: Department of Tumor Immunology, University Hospital  
Nijmegen St. Radboud, Philips van Leydenlaan 25, 6525 EX,  
Nijmegen, Netherlands  
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SOURCE: Cancer Research, (December 15, 2000) Vol. 60, No. 24, pp.  
6995-7001. print.

CODEN: CNREA8. ISSN: 0008-5472.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 31 Jan 2001

Last Updated on STN: 12 Feb 2002

AB **Tyrosinase**-related protein (TRP) 2 belongs to the melanocyte differentiation antigens and has been implicated as a target for immunotherapy of human as well as murine **melanoma**. In the current report, we explored the efficacy of nonmutated epitopes with differential binding affinity for MHC class I, derived from mouse TRP2 to induce CTL-mediated, tumor-reactive immunity in vivo within the established B16 **melanoma** model of C57BL/6 mice. The use of nonmutated TRP2-derived epitopes for vaccination provides a mouse model that closely mimics human **melanoma** without introduction of **xenogeneic** or otherwise foreign antigen. The results demonstrate that vaccination with TRP2 peptide-loaded bone marrow-derived dendritic cells (DCs) results in activation of high avidity TRP2-specific CTLs, displaying lytic activity against both B16 **melanoma** cells and normal melanocytes in vitro. In vivo, protective antitumor immunity against a lethal s.c. B16 challenge was observed upon DC-based vaccination in this fully autologous tumor model. The level of protective immunity positively correlated with the MHC class I binding capacity of the peptides used for vaccination. In contrast, within this autologous model, vaccination with TRP2 peptide in Freund's adjuvant or TRP2-encoding plasmid DNA did not result in protective immunity against B16. Strikingly, despite the observed CTL-mediated melanocyte destruction in vitro, melanocyte destruction in vivo was sporadic and primarily

restricted to minor depigmentation of the vaccination site. These results emphasize the potency of DC-based vaccines to induce immunity against autologous tumor-associated antigen and indicate that CTL-mediated antitumor immunity can proceed without development of adverse autoimmunity against normal tissue

L29 ANSWER 8 OF 13 MEDLINE on STN DUPLICATE 5  
 ACCESSION NUMBER: 2000437812 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10946294  
 TITLE: Relevance of the tumor antigen in the validation of three vaccination strategies for **melanoma**.  
 AUTHOR: Bellone M; Cantarella D; Castiglioni P; Crosti M C; Ronchetti A; Moro M; Garancini M P; Casorati G; Dellabona P  
 CORPORATE SOURCE: Laboratory of Tumor Immunology, Cancer Immunotherapy and Gene Therapy Program, H. San Raffaele Scientific Institute, Milan, Italy.. bellone.matteo@hsr.it  
 SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2000 Sep 1) 165 (5) 2651-6.  
 Journal code: 2985117R. ISSN: 0022-1767.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200009  
 ENTRY DATE: Entered STN: 20000928  
 Last Updated on STN: 20000928  
 Entered Medline: 20000919

AB Many preclinical studies of cancer immunotherapy are based on the testing of a single vaccination strategy in several tumor models. Moreover, most of those studies used **xenogeneic** Ags, which, owing to their high immunogenicity, may not represent realistic models for the validation of cancer immunotherapies. To address these issues, we compared the vaccination efficacy of three well established strategies (i.e., naked DNA; peptide-pulsed dendritic cells (DC), or a mixture of peptide and the Escherichia coli toxin LTR72) using the **xenogeneic** OVA or the naturally expressed **tyrosinase**-related protein 2 (TRP-2) tumor Ag in the B16 **melanoma** model. C57BL/6 mice received one to three s.c. injections of peptide-pulsed DC or DNA, or one to four mucosal administrations of peptide-toxin mixture. One to 2 wk later, the animals were challenged s.c. with B16 or B16 cells expressing OVA (B16-OVA). Vaccination of mice with OVA induced in all cases **melanoma**-specific CTL and protection against B16-OVA. When TRP-2 was used, all three vaccines elicited B16-specific CTL, but only DC pulsed with the immunodominant T cell epitope TRP-2181-188 allowed protection against B16. Even more importantly, a vaccination regimen with TRP-2-pulsed DC, started 24 h after the injection of a lethal number of B16 cells, caused a therapeutic effect in 60% of the challenged animals. Our results strongly emphasize the relevance of the tumor Ag in the definition of immunotherapeutic strategies for cancer, and support the use of peptide-pulsed DC as cancer vaccine in humans.

L29 ANSWER 9 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
 ACCESSION NUMBER: 2000:224990 BIOSIS  
 DOCUMENT NUMBER: PREV200000224990  
 TITLE: The role of representative Th1 and Th2 cytokines (IFN-gamma and IL-4) in the response to **xenogeneic** DNA vaccination with **tyrosinase** related protein-2.  
 AUTHOR(S): Wolchok, Jedd D. [Reprint author]; Srinivasan, Roopa [Reprint author]; Bowne, Wilbur B. [Reprint author];

Perales, Miguel A. [Reprint author]; Blachere, Nathalie E. [Reprint author]; Lewis, Jonathan J. [Reprint author]; Houghton, Alan N. [Reprint author]  
 CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Ctr, New York, NY, USA  
 SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 469. print.  
 Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.  
 ISSN: 0197-016X.  
 DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 31 May 2000  
 Last Updated on STN: 5 Jan 2002

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 STN DUPLICATE 6

ACCESSION NUMBER: 2000:167792 BIOSIS  
 DOCUMENT NUMBER: PREV200000167792  
 TITLE: Genetic immunization of mice with human **tyrosinase**-related protein 2: Implications for the immunotherapy of **melanoma**.  
 AUTHOR(S): Steitz, Julia; Brueck, Juergen; Steinbrink, Kerstin; Enk, Alexander; Knop, Juergen; Tueting, Thomas [Reprint author]  
 CORPORATE SOURCE: Department of Dermatology, J. Gutenberg-University, Langenbeckstr. 1, D-55101, Mainz, Germany  
 SOURCE: International Journal of Cancer, (April 1, 2000) Vol. 86, No. 1, pp. 89-94. print.  
 CODEN: IJCNWA. ISSN: 0020-7136.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 3 May 2000  
 Last Updated on STN: 4 Jan 2002

AB The melanosomal protein TRP2 expressed by melanocytes and most **melanoma** cells is an attractive, clinically relevant model antigen for the experimental development of **melanoma** immunotherapy in mice. A peptide shared by murine and human TRP2 can be recognized by **melanoma**-reactive CTL in C57BL/6 mice, as well as in human **melanoma** patients. Previous experiments demonstrated that gene gun immunization of mice with plasmid DNA encoding autologous murine TRP2 was unable to induce protective immunity against Bl6 **melanoma** cells naturally expressing TRP2. In the present study, we investigated whether the use of cDNA encoding **xenogeneic** human TRP2, which is highly homologous to murine TRP2, would be more effective. Genetic immunization of mice with human TRP2 resulted in coat depigmentation as a sign of autoimmune-mediated destruction of melanocytes and provided significant protection against metastatic growth of Bl6 **melanoma**. Induction of protective immunity was associated with TRP2-reactive antibodies and CD8+ T cells. Furthermore, immunization with recombinant adenovirus was more effective than immunization with plasmid DNA using the gene gun. Our results provide new insights for the development of antigen-specific immunotherapy of **melanoma**.

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 STN DUPLICATE 7

ACCESSION NUMBER: 2000:59901 BIOSIS  
 DOCUMENT NUMBER: PREV200000059901  
 TITLE: Coupling and uncoupling of tumor immunity and autoimmunity.

AUTHOR(S): Bowne, Wilbur B.; Srinivasan, Roopa; Wolchok, Jedd D.;  
Hawkins, William G.; Blachere, Nathalie E.; Dyall, Ruben;  
Lewis, Jonathan J.; Houghton, Alan N. [Reprint author]  
CORPORATE SOURCE: Swim Across America Laboratory, Memorial Sloan-Kettering  
Cancer Center, 1275 York Ave., New York, NY, USA  
SOURCE: Journal of Experimental Medicine, (Dec. 6, 1999) Vol. 190,  
No. 11, pp. 1717-1722. print.  
CODEN: JEMEAU. ISSN: 0022-1007.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 3 Feb 2000  
Last Updated on STN: 3 Jan 2002

AB Self-antigens, in the form of differentiation antigens, are commonly  
recognized by the immune system on **melanoma** and other cancers.  
We have shown previously that active immunization of mice against the  
melanocyte differentiation antigen, a **tyrosinase**-related protein  
(TRP) gp75TRP-1 (the brown locus protein) expressed by **melanomas**  
, could induce tumor immunity and autoimmunity manifested as  
depigmentation. In this system, tumor immunity and autoimmunity were  
mediated by autoantibodies. Here, we characterize immunity against  
another **tyrosinase** family glycoprotein TRP-2 (the slaty locus  
protein), using the same mouse model and method of immunization. As  
observed previously for gp75TRP-1, immunity was induced by DNA  
immunization against a **xenogeneic** form of TRP-2, but not against  
the syngeneic gene, and depended on CD4+ cells. Immunization against  
TRP-2 induced autoantibodies and autoreactive cytotoxic T cells. In  
contrast to immunization against gp75TRP-1, both tumor immunity and  
autoimmunity required CD8+ T cells, but not antibodies. Only autoimmunity  
required perforin, whereas tumor immunity proceeded in the absence of  
perforin. Thus, immunity induced against two closely related autoantigens  
that are highly conserved throughout vertebrate evolution involved  
qualitatively different mechanisms, i.e., antibody versus CD8+ T cell.  
However, both pathways led to tumor immunity and identical phenotypic  
manifestations of autoimmunity.

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STN

ACCESSION NUMBER: 1999:184406 BIOSIS  
DOCUMENT NUMBER: PREV199900184406  
TITLE: IFN-gamma inhibits the antibody response to syngeneic gp75/  
**tyrosinase** related protein-1 induced by DNA  
immunization with **xenogeneic** gp75.  
AUTHOR(S): Wolchok, J. D.; Srinivasan, R.; Bowne, W. B.; Moroi, Y.;  
Lewis, J. J.; Houghton, A. N.  
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY 10021,  
USA  
SOURCE: Proceedings of the American Association for Cancer Research  
Annual Meeting, (March, 1999) Vol. 40, pp. 75. print.  
Meeting Info.: 90th Annual Meeting of the American  
Association for Cancer Research. Philadelphia,  
Pennsylvania, USA. April 10-14, 1999. American Association  
for Cancer Research.  
ISSN: 0197-016X.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 5 May 1999  
Last Updated on STN: 5 May 1999

L29 ANSWER 13 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
STN DUPLICATE 8

ACCESSION NUMBER: 1997:43827 BIOSIS

DOCUMENT NUMBER: PREV199799335815

TITLE: Immune response to a differentiation antigen induced by altered antigen: A study of tumor rejection and autoimmunity.

AUTHOR(S): Naftzger, Clarissa; Takechi, Yoshizumi; Kohda, Hironobu; Hara, Isao; Vijayasaradhi, Setaluri; Houghton, Alan N. [Reprint author]

CORPORATE SOURCE: Swim Across America Lab., Immunol. Program Dep. Med., Meml. Sloan-Kettering Cancer Cent., 1275 York Ave., New York, NY 10021, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1996) Vol. 93, No. 25, pp. 14809-14814.

CODEN: PNASA6. ISSN: 0027-8424.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 28 Jan 1997

Last Updated on STN: 28 Jan 1997

AB Recognition of self is emerging as a theme for the immune recognition of human cancer. one question is whether the immune system can actively respond to normal tissue autoantigens expressed by cancer cells. A second but related question is whether immune recognition of tissue autoantigens can actually induce tumor rejection. To address these issues, a mouse model was developed to investigate immune responses to a melanocyte differentiation antigen, **tyrosinase**-related protein 1 (or gp75), which is the product of the brown locus. In mice, immunization with purified syngeneic gp75 or syngeneic cells expressing gp75 failed to elicit antibody or cytotoxic T-cell responses to gp75, even when different immune adjuvants and cytokines were included. However, immunization with altered sources of gp75 antigen, in the form of either syngeneic gp75 expressed in insect cells or human gp75, elicited autoantibodies to gp75. Immunized mice rejected metastatic **melanomas** and developed patchy depigmentation in their coats. These studies support a model of tolerance maintained to a melanocyte differentiation antigen where tolerance can be broken by presenting sources of altered antigen (e.g., homologous **xenogeneic** protein or protein expressed in insect cells). Immune responses induced with these sources of altered antigen reacted with various processed forms of native, syngeneic protein and could induce both tumor rejection and autoimmunity.